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(71) Applicants *(for all designated States except US)*: **BAYER CORPORATION** [US/US]; 100 Bayer Road, Pittsburgh, PA 15205 (US). **MORPHOSYS AG** [DE/DE]; Lena-Christ-Str. 48, 82152 Martinsried/Munchen (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **PAN, Clark** [US/US]; 22362 Princeton Place, Castro Valley, CA 94552 (US). **KNORR, Andreas, M.** [DE/DE]; Trillser Graben 10, 40699 Erkrath (DE). **SCHAUER, Michael** [DE/DE]; Falkenberg 28, 42113 Wuppetatal (DE). **HIRTH-DIETRICH, Claudia** [DE/DE]; Stockmannsmühle 127, 42115 Wuppertal (DE). **KRAFT, Sabine** [DE/DE]; Planegger Strasse 11 A, 82152 Planegg (DE). **KREBS, Barbara** [DE/DE]; Auf Dem Kamm 13, 51427 Bergsich Galdbach (DE).

(74) Agent: **HEMMENDINGER, Lisa, M.**; Banner & Witcoff, Ltd., 11th floor, 1001 G Street, N.W., Washington, DC 20001-4597 (US).

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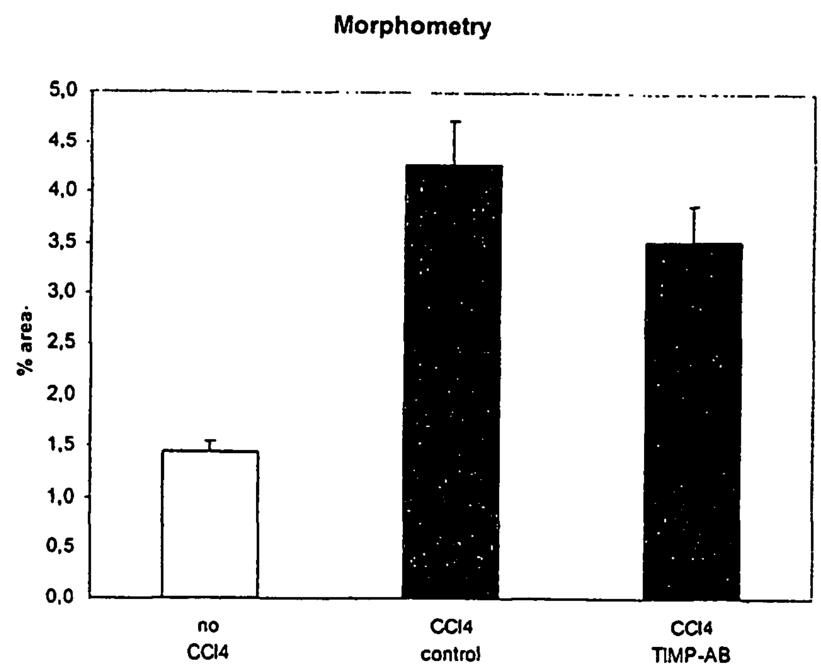
(54) Title: HUMAN TIMP-1 ANTIBODIES



(57) Abstract: Human antibodies that bind to TIMP-1 can be used as reagents to diagnose and treat disorders in which TIMP-1 is elevated, such as liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, colon cancer, lung cancer, and idiopathic pulmonary fibrosis.

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HUMAN TIMP-1 ANTIBODIES

[01] This application claims priority to and incorporates by reference co-pending provisional application Serial No. 60/285,683 filed April 24, 2001.

FIELD OF THE INVENTION

[02] The invention relates to TIMP-1-binding human antibodies.

BACKGROUND OF THE INVENTION

[03] Tissue inhibitors of metalloproteases (TIMPs) inhibit metalloproteases, a family of endopeptide hydrolases. Metalloproteases are secreted by connective tissue and hematopoietic cells, use Zn^{2+} or Ca^{2+} for catalysis, and may be inactivated by metal chelators as well as TIMP molecules. Matrix metalloproteases (MMPs) participate in a variety of biologically important processes, including the degradation of many structural components of tissues, particularly the extracellular matrix (ECM).

[04] Degradation of extracellular matrix tissue is desirable in processes where destruction of existing tissues is necessary, *e.g.*, in embryo implantation (Reponen *et al.*, *Dev. Dyn. 202*, 388-96, 1995), embryogenesis, and tissue remodeling. Imbalance between synthesis and degradation of matrix proteins, however, can result in diseases such as liver fibrosis (Iredale *et al.*, *Hepatology 24*, 176-84, 1996). This imbalance can occur, for example, if levels of TIMPs are increased. Disorders in which TIMP-1 levels of increased include, for example, liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, and colon cancer. *See, e.g.*, Inokubo

et al., *Am. Heart J. 141*, 211-17, 2001; Ylisirnio *et al.*, *Anticancer Res. 20*, 1311-16, 2000; Holten-Andersen *et al.*, *Clin. Cancer Res. 6*, 4292-99, 2000; Holten-Andersen *et al.*, *Br. J. Cancer 80*, 495-503, 1999; Peterson *et al.*; *Cardiovascular Res. 46*, 307-15, 2000; Arthur *et al.*, *Alcoholism: Clinical and Experimental Res. 23*, 840-43, 1999; Iredale *et al.*, *Hepatol. 24*, 176-84, 1996.

[06] There is a need in the art for reagents and methods of inhibiting TIMP-1 activity, which can be used to provide therapeutic effects.

BRIEF SUMMARY OF THE INVENTION

[07] It is an object of the present invention to provide reagents and methods of inhibiting TIMP-1 activity. This and other objects of the invention are provided by one or more of the embodiments described below.

[08] One embodiment of the invention is a purified preparation of a human antibody, wherein the antibody binds to a tissue inhibitor of metalloprotease-1 (TIMP-1) and neutralizes a matrix metalloprotease (MMP)-inhibiting activity of the TIMP-1.

[09] Another embodiment of the invention is a purified preparation of a first human antibody which comprises a VHCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360.

[10] Still another embodiment of the invention is a purified preparation of a first human antibody which comprises a VLCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379.

[11] Yet another embodiment of the invention is a purified preparation of a first human antibody which has TIMP-1 binding and MMP-inhibiting activity characteristics of a second human antibody. The second antibody comprises a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5

and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

[12] Even another embodiment of the invention is a purified preparation of a human antibody comprising a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ

ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

[13] A further embodiment of the invention is a purified preparation of a human antibody which comprises a heavy chain and a light chain amino acid pair selected from the group consisting of SEQ ID NOS:140 and 97, SEQ ID NOS:141 and 98, SEQ ID NOS:142 and 99, SEQ ID NOS:143 and 100, SEQ ID NOS:144 and 101, SEQ ID NOS:145 and 102, SEQ ID NOS:146 and 103, SEQ ID NOS:142 and 97, SEQ ID NOS:142 and 98, SEQ ID NOS:142 and 100, SEQ ID NOS:142 and 101, SEQ ID NOS:142 and 102, SEQ ID NOS:142 and 103, SEQ ID NOS:146 and 97, SEQ ID NOS:146 and 98, SEQ ID NO:146 and 100, SEQ ID NOS:146 and 101, SEQ ID NOS:148 and 104, SEQ ID NOS:148 and 105, SEQ ID NOS:149 and 106, SEQ ID NOS:150 and 107, SEQ ID NOS:151 and 108, SEQ ID NOS:152 and 109, SEQ ID NOS:153 and 110, SEQ ID NOS:154 and 111, SEQ ID NOS:155 and 112, SEQ ID NOS:156 and 113, SEQ ID NOS:157 and 114, SEQ ID NOS:158 and 115, SEQ ID NOS:159 and 116, SEQ ID NOS:160 and 117, SEQ ID NOS:161 and 118, SEQ ID NOS:162 and 119, SEQ ID NOS:163 and 120, SEQ ID NOS:164 and 121, SEQ ID NOS:165 and 122, SEQ ID NOS:166 and 123, SEQ ID NOS:167 and 124, SEQ ID NOS:168 and 125, SEQ ID NOS:169 and 126, SEQ ID NOS:170 and 127, SEQ ID NOS:171 and 128, SEQ ID NOS:172 and 129, SEQ ID NOS:173 and 130, SEQ ID NOS:174 and 131, SEQ ID NOS:175 and 132, SEQ ID NOS:176 and 133, SEQ ID NOS:177 and 134, SEQ ID NOS:178 and 135, SEQ ID NOS:179 and 136, SEQ ID NOS:180 and 137, SEQ ID NOS:181 and 138, and SEQ ID NOS:182 and 139.

[14] Another embodiment of the invention is a pharmaceutical composition comprising a human antibody and a pharmaceutically acceptable carrier. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[15] Yet another embodiment of the invention is a purified polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[16] Even another embodiment of the invention is a purified polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[17] Still another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[18] A further embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.

[19] Another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID

NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[20] Yet another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.

[21] Still another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.

[22] Even another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182. The heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.

[23] A further embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain

having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

[24] Another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139. The light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.

[25] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[26] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.

[27] Still another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[28] A further embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.

[29] Another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.

[30] Still another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182. The heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.

[31] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human

antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

[32] Even another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139. The light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.

[33] A further embodiment of the invention is a method of making a human antibody. The host cell of claim 43 is cultured under conditions whereby the antibody is expressed. The human antibody is purified from the host cell culture.

[34] Another embodiment of the invention is a method of decreasing an MMP-inhibiting activity of a TIMP-1. The TIMP-1 is contacted with a human antibody that binds to the TIMP-1. The MMP-inhibiting activity of the TIMP-1 is decreased relative to MMP-inhibiting activity of the TIMP-1 in the absence of the antibody.

[35] Still another embodiment of the invention is a method of ameliorating symptoms of a disorder in which TIMP-1 is elevated. An effective amount of a human antibody which neutralizes an MMP-inhibiting activity of the TIMP-1 is administered to a patient having the disorder. Symptoms of the disorder are thereby ameliorated.

[36] A further embodiment of the invention is a method of detecting a TIMP-1 in a test preparation. The test preparation is contacted with a human antibody that specifically binds to the TIMP-1. The test preparation is assayed for the presence of an antibody-TIMP-1 complex.

[37] Even another embodiment of the invention is a method to aid in diagnosing a disorder in which a TIMP-1 level is elevated. A sample from a patient suspected of having the disorder is contacted with a human antibody that binds to TIMP-1. The sample is assayed for the presence of an antibody-TIMP-1 complex. Detection of an amount of the complex which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.

[38] The invention thus provides human antibodies which bind to TIMP-1 and neutralize MMP-inhibiting activity of TIMP-1. These antibodies can be used, *inter alia*, in diagnostic and therapeutic methods.

BRIEF DESCRIPTION OF THE FIGURES

[39] FIG. 1. Protein sequences encoded by the HuCAL® V_H and V_L Fab master genes. Seven V_H and V_L sequences are aligned, and the approximate location of restriction endonuclease sites introduced into the corresponding DNA sequences are indicated. The numbering is according to VBASE except for the gap in Vl position 9. In VBASE the gap is set at position 10. See also Chothia *et al.* (1992) *J. Mol. Biol. 227*, 776-798, Tomlinson *et al.* (1995) *EMBO J. 14*, 4628-4638 and Williams *et al.* (1996) *J. Mol. Biol. 264*, 220-232).

[40] FIG. 2. Nucleotide sequences of the HuCAL® V_H and V_L Fab master genes.

[41] FIG. 3. Fab display vector pMORPH® 18 Fab 1.

[42] FIG. 4. Vector map of pMORPH® x9Fab1_FS.

[43] FIG. 5. Sequence comparison between human and rat TIMP-1. Sequence regions in bold were used for peptide synthesis. Residues that make stronger direct contacts with MMP-3 are italicized, and residues that make weaker direct contacts with MMP-3 are underlined (Gomis-Ruth *et al.*, 1997).

Methods of decreasing MMP-inhibiting activity of human TIMP-1

[88] The invention provides methods of decreasing an MMP-inhibiting activity of human or rat TIMP-1. Such methods can be used therapeutically, as described below, or in a research setting. Thus, the methods can be carried out in a cell-free system, in a cell culture system, or *in vivo*. *In vivo* methods of decreasing MMP-inhibiting activity of human or rat TIMP-1 are described below.

[89] Human TIMP-1 is contacted with a human antibody that binds to the human TIMP-1, thereby decreasing the MMP-inhibiting activity of the human TIMP-1 relative to human TIMP-1 activity in the absence of the antibody. The antibody can be added directly to the cell-free system, cell culture system, or to an animal subject or patient, or can be provided by means of an expression vector encoding the antibody.

Diagnostic methods

[90] The invention also provides diagnostic methods, with which human or rat TIMP-1 can be detected in a test preparation, including without limitation a sample of serum, lung, liver, heart, kidney, colon, a cell culture system, or a cell-free system (*e.g.*, a tissue homogenate). Such diagnostic methods can be used, for example, to diagnose disorders in which TIMP-1 is elevated. Such disorders include, but are not limited to, liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute cardiac syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, lung cancer, colon cancer, and idiopathic pulmonary fibrosis. When used for diagnosis, detection of an amount of the antibody-TIMP-1 complex in a test sample from a patient which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.

[91] The test preparation is contacted with a human antibody of the invention, and the test preparation is then assayed for the presence of an antibody-TIMP-1 complex. If desired, the human antibody can comprise a detectable label, such as a fluorescent, radioisotopic,

chemiluminescent, or enzymatic label, such as horseradish peroxidase, alkaline phosphatase, or luciferase.

[92] Optionally, the antibody can be bound to a solid support, which can accommodate automation of the assay. Suitable solid supports include, but are not limited to, glass or plastic slides, tissue culture plates, microtiter wells, tubes, silicon chips, or particles such as beads (including, but not limited to, latex, polystyrene, or glass beads). Any method known in the art can be used to attach the antibody to the solid support, including use of covalent and non-covalent linkages, passive absorption, or pairs of binding moieties attached to the antibody and the solid support. Binding of TIMP-1 and the antibody can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and microcentrifuge tubes.

Therapeutic methods

[93] The invention also provides methods of ameliorating symptoms of a disorder in which TIMP-1 is elevated. These disorders include, without limitation, liver fibrosis alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, colon cancer, and scarring. *See, e.g.*, Inokubo *et al.*, *Am. Heart J. 141*, 211-17, 2001; Ylisirnio *et al.*, *Anticancer Res. 20*, 1311-16, 2000; Holten-Andersen *et al.*, *Clin. Cancer Res. 6*, 4292-99, 2000; Holten-Andersen *et al.*, *Br. J. Cancer 80*, 495-503, 1999; Peterson *et al.*, *Cardiovascular Res. 46*, 307-15, 2000; Arthur *et al.*, *Alcoholism: Clinical and Experimental Res. 23*, 840-43, 1999; Iredale *et al.*, *Hepatol. 24*, 176-84, 1996.

[94] Human antibodies of the invention are particularly useful for treating liver fibrosis. All chronic liver diseases cause the development of fibrosis in the liver. Fibrosis is a programmed uniform wound healing response. Toxic damage or injury caused by foreign proteins cause the deposition of extracellular matrix such as collagen, fibronectin, and laminin. Liver fibrosis and cirrhosis can be caused by chronic degenerative diseases

of the liver such as viral hepatitis, alcohol hepatitis, autoimmune hepatitis, primary biliary cirrhosis, cystic fibrosis, hemochromatosis, Wilson's disease, and non-alcoholic steato-hepatitis, as well as chemical damage.

[95] Altered degradation and synthesis of extracellular matrix (particularly collagens) play central roles in pathogenesis of liver fibrosis. In the early phases, hepatic stellate cells (HSC) are initially activated and release matrix metalloproteases with the ability to degrade the normal liver matrix. When HSC are fully activated, there is a net down-regulation of matrix degradation mediated by increased synthesis and extracellular release of tissue inhibitors of metalloprotease (TIMP)-1 and -2. The dynamic regulation of activity of metalloproteases during liver fibrosis makes them and their inhibitors targets for therapeutic intervention.

[96] Human antibodies of the invention are also particularly useful for treating lung fibrosis. Lung airway fibrosis is a hallmark of airway remodeling in patients with chronic asthma, so human antibodies of the invention are also particularly useful for chronic asthma. Airway remodeling is a well-recognized feature in patients with chronic asthma. TIMP-1 but not TIMP-2 levels were significantly higher in untreated asthmatic subjects than in glucocorticoid-treated subjects or controls ($p < 0.0001$), and were far greater than those of MMP-1, MMP-2, MMP-3, and MMP-9 combined (Mautino *et al.*, Am J Respir Crit Care Med 1999 160:324-330). TIMP-1 mRNA and protein expression are selectively and markedly increased in a murine model of bleomycin-induced pulmonary fibrosis (Am. J. Respir. Cell Mol. Biol. 24:599-607, 2001). This specific elevation of TIMP-1 without increase in MMPs in asthma patients suggests that inhibition of TIMP-1 by an antibody can restore normal collagen degradation in the lung.

[97] Human antibodies of the invention are also particularly useful for treating cancer. TIMP-1 protein has been found to be elevated in plasma of colon (Holten-Andersen et al., Br J Cancer 1999, 80:495-503) and prostate (Jung et al., Int J Cancer, 1997, 74:220-223) cancer patients, and high TIMP-1 plasma level correlates with poor clinical outcome of

colon cancer (Holten-Andersen et al., Clin Cancer Res 2000 6:4292-4299). TIMP-1 induces dose-dependent proliferation of breast tumorigenic clonal cell line and tyrosine phosphorylation (Luparello et al, Breast Cancer Res Treat, 1999, 54:235-244). Therefore, the use of antibody against TIMP-1 may block its ability to induce cancer.

[98] Human TIMP-1 antibodies can be used to prevent or diminish scar formation, such as scar formation after surgery (particularly ophthalmic surgery) or injury (such as a burn, scrape, crush, cut or tear injury).

[99] In one embodiment of the invention, a therapeutically effective dose of a human antibody of the invention is administered to a patient having a disorder in which TIMP-1 is elevated, such as those disorders described above. Symptoms of the disorder, including deposition of extracellular matrix, as well as loss of tissue or organ function, are thereby ameliorated.

Determination of a Therapeutically Effective Dose

[100] The determination of a therapeutically effective dose is well within the capability of those skilled in the art. A therapeutically effective dose refers to that amount of human antibody that reduces MMP-inhibiting activity of the TIMP-1 relative to the activity which occurs in the absence of the therapeutically effective dose.

[101] The therapeutically effective dose can be estimated initially either in cell culture assays or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model also can be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. A rat liver fibrosis model is described in Example 6.

[102] Therapeutic efficacy and toxicity, *e.g.*, ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population) of a human antibody, can be determined by standard pharmaceutical procedures in cell cultures or experimental

animals. The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50}.

[103] Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[104] The exact dosage will be determined by the practitioner, in light of factors related to the patient who requires treatment. Dosage and administration are adjusted to provide sufficient levels of the human antibody or to maintain the desired effect. Factors that can be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions can be administered every 3 to 4 days, every week, or once every two weeks depending on the half-life and clearance rate of the particular formulation.

[105] Polynucleotides encoding human antibodies of the invention can be constructed and introduced into a cell either *ex vivo* or *in vivo* using well-established techniques including, but not limited to, transferrin-polycation-mediated DNA transfer, transfection with naked or encapsulated nucleic acids, liposome-mediated cellular fusion, intracellular transportation of DNA-coated latex beads, protoplast fusion, viral infection, electroporation, "gene gun," and DEAE- or calcium phosphate-mediated transfection.

[106] Effective *in vivo* dosages of an antibody are in the range of about 5 mg to about 50 mg/kg, about 50 mg to about 5 mg/kg, about 100 mg to about 500 mg/kg of patient body weight, and about 200 to about 250 mg/kg of patient body weight. For administration of polynucleotides encoding the antibodies, effective *in vivo* dosages are in the range of

about 100 ng to about 200 ng, 500 ng to about 50 mg, about 1 mg to about 2 mg, about 5 mg to about 500 mg, and about 20 mg to about 100 mg of DNA.

[107] The mode of administration of human antibody-containing pharmaceutical compositions of the invention can be any suitable route which delivers the antibody to the host. Pharmaceutical compositions of the invention are particularly useful for parenteral administration, *i.e.*, subcutaneous, intramuscular, intravenous, or intranasal administration.

[108] All patents, patent applications, and references cited in this disclosure are expressly incorporated herein by reference. The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific examples, which are provided for purposes of illustration only and are not intended to limit the scope of the invention.

EXAMPLE 1

Construction of a Human Combinatorial Antibody Library (HuCAL® Fab 1)

[109] *Cloning of HuCAL® Fab 1.* HuCAL® Fab 1 is a fully synthetic, modular human antibody library in the Fab antibody fragment format. HuCAL® Fab 1 was assembled starting from an antibody library in the single-chain format (HuCAL® -scFv; Knappik *et al.*, *J. Mol. Biol. 296*, 55, 2000). HuCAL® Fab 1 was cloned into a phagemid expression vector pMORPH® 18 Fab1 (FIG. 3). This vector comprises the Fd fragment with a phoA signal sequence fused at the C-terminus to a truncated gene III protein of filamentous phage, and further comprises the light chain VL-CL with an ompA signal sequence. Both chains are under the control of the lac operon. The constant domains C?, C?, and CH are synthetic genes fully compatible with the modular system of HuCAL® (Knappik *et al.*, 2000).

[110] First, the V? and V? libraries were isolated from HuCAL®-scFv. V?1 fragments were amplified by 15 PCR cycles (Pwo polymerase) with primers 5'-

GTGGTGGTTCCGATATC-3′ (SEQ ID NO:380) and 5′- AGCGTCACA-CTCGGTGCGGCTTTCGGCTGGCCAAGAACGGTTA-3′ (SEQ ID NO:381). PCR-products were digested with EcoRV / DraIII and gel-purified. VL?-chains were obtained by restriction digest with EcoRV / BsiWI and gel-purified. These V? and V? libraries were cloned into pMORPH® 18 Fab1 cut with *Eco*RV / *Dra*III and *Eco*RV / *Bsi*WI, respectively. After ligation and transformation in *E. coli* TG-1, library sizes of 4.14×10^8 and 1.6×10^8, respectively, were obtained, in both cases exceeding the V? diversity of HuCAL®-scFv.

[111] Similarly, the VH library was isolated from HuCAL®-scFv by restriction digest using *Sty*I / *Mun*I. This VH library was cloned into the pMORPH® 18-V? and V? libraries cut with *Sty*I / *Mun*I. After ligation and transformation in *E. coli* TG-1, a total library size of 2.09×10^{10} was obtained, with 67% correct clones (as identified by sequencing of 207 clones).

[112] *Phagemid rescue, phage amplification and purification.* HuCAL® Fab was amplified in 2 x TY medium containing 34 µg/ml chloramphenicol and 1 % glucose (2 x TY-CG). After helper phage infection (VCSM13) at 37°C at an OD_{600} of about 0.5, centrifugation and resuspension in 2 x TY / 34 µg/ml chloramphenicol/ 50 µg/ml kanamycin, cells were grown overnight at 30°C. Phage were PEG-precipitated from the supernatant (Ausubel *et al.*, 1998), resuspended in PBS/20% glycerol, and stored at –80°C. Phage amplification between two panning rounds was conducted as follows: mid-log phase TG1-cells were infected with eluted phage and plated onto LB-agar supplemented with 1% of glucose and 34 µg/ml of chloramphenicol. After overnight incubation at 30°C, colonies were scraped off and adjusted to an OD_{600} of 0.5. Helper phage were added as described above.

EXAMPLE 2

Solid phase panning

[113] Wells of MaxiSorp™ microtiter plates (Nunc) were coated with rat- or human TIMP protein diluted to 50 μg/ml dissolved in PBS (2 μg/well). After blocking with 5% non-fat dried milk in PBS, 1–5 x 10^{12} HuCAL® Fab phage purified as above were added for 1h at 20°C. After several washing steps, bound phage were eluted by pH-elution with 100 mM triethylamine and subsequent neutralization with 1M TRIS-Cl pH 7.0. See Krebs *et al.*, *J. Immunol. Meth. 254*, 67, 2001. Two to three rounds of panning were performed with phage amplification conducted between each round as described above.

EXAMPLE 3

Solution panning

[114] Biotinylated antigen was diluted to 40 nM in PBS, 1013 HuCAL®-Fab 1 phage were added and incubated for 1 h at 20°C. Phage-antigen complexes were captured on Neutravidin plates (Pierce). After several washing steps, bound phages were eluted by different methods (Krebs *et al.*, 2001). Two rounds of panning were routinely performed.

EXAMPLE 4

Subcloning of selected Fab fragments for expression

[115] The Fab-encoding inserts of the selected HuCAL® Fab 1 fragments were subcloned into the expression vector pMORPH® x7_FS (Knappik *et al.*, *J. Mol. Biol. 296*, 55, 2000) to facilitate rapid expression of soluble Fab. The DNA preparation of the selected HuCAL® Fab 1 clones was digested with *Xba*I / *Eco*RI, thus cutting out the Fab encoding insert (ompA-VL and phoA-Fd). Subcloning of the purified inserts into the *Xba*I / *Eco*RI cut vector pMORPH® x7, previously carrying a scFv insert, produces a Fab expression vector designated pMORPH® x9_Fab1_FS (FIG. 4). Fabs expressed in this vector carry two C-terminal tags (FLAG™ and Strep-tagII) for detection and purification.

EXAMPLE 5

Identification of TIMP-binding Fab fragments by ELISA

[116] The wells of 384-well Maxisorp ELISA plates were coated with 20 µl/well solutions of rat TIMP or human TIMP at a concentration of 5 µg/ml diluted in coating buffer. Expression of individual Fab in *E. coli* TG-1 from expression vector pMORPH® x9_FS was induced with 0.5 mM IPTG for 12 h at 30°C. Soluble Fab was extracted from the periplasm by osmotic shock (Ausubel *et al.*, 1998) and used in an ELISA. The Fab fragment was detected after incubation with alkaline phosphatase-conjugated anti-Fab antibody (Dianova), followed by development with Attophos substrate (Roche) and measurement at Ex450 nm / Em535 nm. Values at 370 nm were read out after addition of horseradish peroxidase-conjugated anti-mouse IgG antibody and POD soluble substrate (Roche Diagnostics).

EXAMPLE 6

Expression and purification of HuCAL®-Fab 1 antibodies in E. coli

[117] Expression of Fab fragments encoded by pMORPH® x9_FS in TG-1 cells was carried out in shaker flask cultures with 1 liter of 2xTY medium supplemented with 34 µg/ml chloramphenicol. After induction with 0.5 mM IPTG, cells were grown at 22°C for 16 h. Periplasmic extracts of cell pellets were prepared, and Fab fragments were isolated by Strep-tactin® chromatography (IBA, Goettingen, Germany). The apparent molecular weights were determined by size exclusion chromatography (SEC) with calibration standards. Concentrations were determined by UV-spectrophotometry.

EXAMPLE 7

Construction of HuCAL® immunoglobulin expression vectors

[118] *Heavy chain cloning*. The multiple cloning site of pcDNA3.1+ (Invitrogen) was removed (*Nhe*I / *Apa*I), and a stuffer compatible with the restriction sites used for HuCAL® design

was inserted for the ligation of the leader sequences (*Nhe*I / *Eco*RI), VH-domains (*Eco*RI / *Blp*I), and the immunoglobulin constant regions (*Blp*I / *Apa*I). The leader sequence (EMBL M83133) was equipped with a Kozak sequence (Kozak, 1987). The constant regions of human IgG_1 (PIR J00228), IgG_4 (EMBL K01316), and serum IgA_1 (EMBL J00220) were dissected into overlapping oligonucleotides with lengths of about 70 bases. Silent mutations were introduced to remove restriction sites non-compatible with the HuCAL® design. The oligonucleotides were spliced by overlap extension-PCR.

[119] *Light chain cloning*. The multiple cloning site of pcDNA3.1/Zeo+ (Invitrogen) was replaced by two different stuffers. The ?-stuffer provided restriction sites for insertion of a ?-leader (*Nhe*I / *Eco*RV), HuCAL®-scFv V?-domains (*Eco*RV / *Bsi*WI,) and the ?-chain constant region (*Bsi*WI / *Apa*I). The corresponding restriction sites in the ?-stuffer were *Nhe*I / *Eco*RV (?-leader), *Eco*RV / *Hpa*I (V?- domains), and *Hpa*I / *Apa*I (?-chain constant region). The ?-leader (EMBL Z00022) as well as the ?-leader (EMBL L27692) were both equipped with Kozak sequences. The constant regions of the human ?- (EMBL J00241) and ?-chain (EMBL M18645) were assembled by overlap extension-PCR as described above.

[120] *Generation of IgG-expressing CHO-cells*. CHO-K1 cells were co-transfected with an equimolar mixture of IgG heavy and light chain expression vectors. Double-resistant transfectants were selected with 600 µg/ml G418 and 300 µg/ml Zeocin (Invitrogen) followed by limiting dilution. The supernatant of single clones was assessed for IgG expression by capture-ELISA (see below). Positive clones were expanded in RPMI-1640 medium supplemented with 10% ultra-low IgG-FCS (Life Technologies). After adjusting the pH of the supernatant to 8.0 and sterile filtration, the solution was subjected to standard protein A column chromatography (Poros 20 A, PE Biosystems).

EXAMPLE 8

Design of the CDR3 libraries

[121] *V? positions 1 and 2.* The original HuCAL® master genes were constructed with their authentic N-termini: V?l1: QS (CAGAGC), V?l2: QS (CAGAGC), and V?l3: SY (AGCTAT). Sequences containing these amino acids are shown in WO 97/08320. During HuCAL® library construction, the first two amino acids were changed to DI to facilitate library cloning (*Eco*RI site). All HuCAL® libraries contain V?l genes with the *Eco*RV site GATATC (DI) at the 5'-end. All HuCAL® kappa genes (master genes and all genes in the library) contain DI at the 5'-end.

[122] *VH position 1.* The original HuCAL® master genes were constructed with their authentic N-termini: VH1A, VH1B, VH2, VH4, and VH6 with Q (=CAG) as the first amino acid and VH3 and VH5 with E (=GAA) as the first amino acid. Sequences containing these amino acids are shown in WO 97/08320. In the HuCAL® Fab 1 library, all VH chains contain Q (=CAG) at the first position.

[123] *V?1/V?3 position 85.* Because of the cassette mutagenesis procedure used to introduce the CDR3 library (Knappik *et al., J. Mol. Biol. 296*, 57-86, 2000), position 85 of V?1 and V?3 can be either T or V. Thus, during HuCAL® scFv 1 library construction, position 85 of V?1 and V?3 was varied as follows: V?1 original, 85T (codon ACC); V?1 library, 85T or 85V (TRIM codons ACT or GTT); V?3 original, 85V (codon GTG); V?3 library, 85T or 85V (TRIM codons ACT or GTT); the same applies to HuCAL® Fab1.

[124] *CDR3 design.* All CDR3 residues which were kept constant are indicated in FIG. 1.

[125] *CDR3 length.* The designed CDR3 length distribution is as follows. Residues which were varied are shown in brackets (x) in FIG. 1. V kappa CDR3, 8 amino acid residues (position 89 to 96) (occasionally 7 residues), with Q90 fixed; V lambda CDR3, 8 to 10 amino acid residues (position 89 to 96) (occasionally 7-10 residues), with Q89, S90, and

D92 fixed; and VH CDR3, 5 to 28 amino acid residues (position 95 to 102) (occasionally 4-28), with D101 fixed.

EXAMPLE 9

Chronic carbon tetrachloride-induced liver fibrosis

[126] Sprague Dawley rats (200-220 g) are used in an *in vivo* model of liver fibrosis. To maximally induce microsomal metabolism of carbon tetrachloride metabolism, animals receive 1 g/l isoniazid with their drinking water starting one week before the administration of carbon tetrachloride. Carbon tetrachloride (1:1 in mineral oil) is administered orally every fifth day at a dose of 0.2 ml/100 g body weight. A human TIMP-1 antibody is administered intravenously, either once or repeatedly, during the period of carbon tetrachloride treatment. Necropsy is performed after 5-7 weeks of treatment. McLean *et al.*, *Br. J. Exp. Pathol. 50*, 502-06, 1969.

[127] Transverse cylinders of liver tissue are cut from the right liver lobe, fixed in formaldehyde, and embedded in paraffin. The amount of fibrosis in the liver is indicated by the picrosirius red-stained fibrotic areas. Picrosirius-positive areas are determined in several centrilobular fields in each section. Parameters of color detection are standardized and kept constant throughout the experiment. The field are selected using a standardized grid which covers an area of 31 mm2. A Leica Quantimed 500 MC system is used for morphometry.

EXAMPLE 10

Hydroxyproline determination

[128] The method of Prockop & Udenfried, *Anal. Biochem. 1*, 228-39, 1960, can be used to determine hydroxyproline is liver tissues, with the following modifications. Liver specimens of 60-90 mg wet weight are dried and hydrolyzed in 6 N HCl at 100 °C for 17 h. The hydrolyzed material is dried and reconstituted in 5 ml of deionized water. Two

hundred microliters of this hydrolysate are mixed with 200 ml of ethanol and 200 ml chloramin T solution (0.7 % in citrate buffer [5.7 g sodium acetate, 3.75 g trisodium citrate, 0.55 g citric acid, 38.5 ml ethanol, made up to 100 ml with water]) and allowed to oxidize for 20 min at room temperature. Four hundred microliters of Ehrlich's reagent (12 g p-dimethylaminobenzldehyde in 40 ml ethanol and 2.7 ml H_2SO_4) are added. After incubation for 3 h at 35 °C, absorbance at 573 nm is measured.

EXAMPLE 11

Affinity determination by surface plasmon resonance measurements (BIAcore™)

[129] For affinity determination, monomeric fractions of affinity and SEC purified Fab fragments or purified IgG1 molecules were used. All experiments were conducted in HBS buffer at a flow rate of 20 µl/min at 25°C on a BIAcore™ instrument. Antigens in 100 mM sodium acetate pH 5.0 were coupled to a CM 5 sensor chip using standard EDC-NHS coupling chemistry. Applying 3-4 µl of 5 µg/ml TIMP-1 typically resulted in 500 resonance units for kinetic measurements. All sensograms were fitted globally using BIA evaluation software. For monovalent Fab fragments a monovalent fit (Langmuir binding) and for IgGs a bivalent fit was applied.

EXAMPLE 12

IC_{50} determination in human TIMP-1/human MMP-1 and rat TIMP-1/rat MMP-13 assay

[130] Purified Fab fragments or IgGs were used for IC_{50} determination. Antibodies were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM or 0.4 nM for modified in human TIMP-1/human MMP-1 assay), MMP (final conc. 1.2 nM or 0.4 nM for modified in human TIMP-1/human MMP-1 assay), and peptide substrate (final conc. 50 µM) and incubation for 1-3 h at 37°C, fluorescence at Ex320 nm/Em430 nm was measured.

[131] The following controls were included in the assay and used as reference values for IC_{50} determination:

A: MMP + substrate: this value was defined as 100% MMP activity in absence of antibody and TIMP.

B: MMP + TIMP + substrate: this value was defined as maximum inhibition achieved in the assay and calculated as a % of total MMP activity.

[132] To define the concentration of antibody that resulted in 50% reversal of inhibition (IC_{50}), the following procedure was used:

- The value for 50% reversal of inhibition (expressed as % activity MMP) was calculated as: $Y= [(A - B)/2] + B$.
- MMP activity was plotted against concentration of antibody in the assay.
- The concentration of antibody that results in 50% reversal of inhibition (Y) was read on the x-axis and defined as IC_{50}.
- Error bars in the graphs were derived from triplicate wells in one assay.
- Standard deviations for IC_{50} values were calculated from 3 independent assays.

EXAMPLE 13

Affinity maturation of selected Fab by stepwise exchange of CDR cassettes

[133] To increase affinity and biological activity of selected antibody fragments, CDR regions were optimized by cassette mutagenesis using trinucleotide directed mutagenesis (Virnekäs *et al.*, 1994). Fab fragments in expression vector pMORPH® x9 were cloned into phagemid vector pMORPH® _18 using *Eco*RI / *Xba*I restriction sites. CDR cassettes containing several diversified positions were synthesized and cloned into Fab fragments in pMORPH® _18 using unique restriction sites (Knappik *et al.*, 2000). Affinity

maturation libraries were generated by transformation into *E. coli* TOP10F, and phage were prepared as described above. Phage displaying Fab fragments with improved affinity were selected by 2-3 rounds solution panning using stringent washing conditions (*e.g.*, competition with 1 μM non-biotinylated antigen or washing for up to 48 h with frequent buffer exchange) and limited amounts of antigen (0.04 – 4 nM). Seventeen human TIMP-1 antibodies were tested for affinity to human TIMP-1 (with some tested for affinity to rat TIMP-1) using a BIAcore™ assay. The K_d of these antibodies for human TIMP-1 and rat TIMP-1 are shown in Table 1.

Table 1. Overview of species cross-reactive Fab

Fab	Monovalent K_D human TIMP-1	Monovalent K_D rat TIMP-1	IC_{50} in human protease assay	IC_{50} in rat protease assay
MS-BW-25	25+/- 16 nM*	4517 +/- 2400 nM	115 +/- 15 nM	> 300 nM
MS-BW-27	~74 nM	~ 3200 nM	Non blocking	
MS-BW-21	520+/- 20 nM	36 +/- 2 nM	> 300 nM	67 +/- 5nM
MS-BW-38	~3 nM	~353 nM	~11 nM	> 300 nM
MS-BW-39	~7500 nM	~108 nM	> 100 nM	> 100 nM

* In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 14

Screening for Fab with improved off-rates by koff ranking using surface plasmon resonance

[134] Phage eluted after solution panning were used to infect *E. coli* TG-1 and plated on agar plates containing 34 µg/ml chloramphenicol. Clones were picked into 96 well plates and used to produce Fab fragments. On the same plate, parental clones were inoculated as controls. Soluble Fab was extracted from the periplasm by osmotic shock (Ausubel *et al.*, 1998) and used for koff ranking in BIAcore™.

[135] All measurements were conducted in HBS buffer at a flow rate of 20 µl/min at 25°C on a BIAcore™ instrument. Antigens in 100 mM sodium acetate pH 4.5 were coupled to a CM 5 sensor chip using standard EDC-NHS coupling chemistry. Applying 10 µl of 25 µg/ml TIMP-1 typically resulted in 5000 resonance units for koff ranking. All sensograms were fitted using BIA evaluation software. Clones with improved off rate were selected by comparison to parental clones.

EXAMPLE 15

Generation of species cross-reactive antibodies

[136] To maximize the likelihood of obtaining blocking antibodies that are cross-reactive between human and rat TIMP-1, alternating pannings were carried out on rat and human protein. Additionally, all antibodies selected by pannings on solely the human or rat TIMP-1 protein were analyzed for cross-reactivity in order to check for cross-reactive antibodies that might be selected by chance. Antibodies selected from these pannings were analyzed for cross-reactivity in ELISA using crude *E. coli* extracts. Cross-reactive antibodies in this assay were subjected to expression in 1-liter scale followed by purification. Purified antibodies were tested for cross-reactivity in BIAcore™ and protease assays (Table 1).

[137] As shown in Table 1, a total of five different Fab cross-reactive with human and rat TIMP-1 were generated. BIAcore™ measurements revealed that although these antibodies clearly bind to human and rat TIMP-1, affinities for both species differ by at least a factor of 50. An antibody used for human therapy or in an animal model should have an affinity to the target protein in the low nanomolar, preferably in the sub-nanomolar range. As none of the above-described antibodies had affinities in this range for both species, these antibodies were not considered useful for further experiments or development.

EXAMPLE 16

Generation of blocking antibodies against human TIMP-1

[138] To generate blocking antibodies against human TIMP-1, the HuCAL®-Fab 1 library was used for antibody selection (AutoPan®) on purified TIMP-1 protein followed by subcloning and expression of the selected Fab fragments in *E. coli*. Crude antibody-containing *E. coli* extracts were used for primary antibody characterization in ELISA (AutoScreen®). Purified Fab proteins were subjected to further characterization in ELISA, TIMP-1/MMP-1 assay and BIAcore™. A total of 6100 clones were analyzed in AutoScreen®, 670 of them showed binding to human TIMP-1. Sequence analysis revealed that in total seven unique antibody clones had been selected (Table 2). For these seven Fab clones, the affinities measured in BIAcore™ were in the range of 10 – 180 nM (Table 4). When tested in the human protease assay, five of them were able to block the interaction between human TIMP-1 and MMP-1. The concentration of monovalent Fab needed to reverse the inhibitory effect of human TIMP-1 on human MMP-1 activity by 50% (IC_{50}) was in the range of 11 - 100 nM (Table 2). The most active Fab clones are MS-BW-3 (K_d 13 nM; IC_{50} 11 nM) and MS-BW-28 (K_d 10 nM; IC_{50} 22 nM).

[139] A striking feature of antibodies selected against human TIMP-1 is that they all exhibit the combination VH3l2 and a relatively short VH-CDR3 region, predominantly four amino acids (see Table 2). The HCDR3 cassettes assembled for the HuCAL®-Fab 1 library

were designed to achieve a length distribution ranging from 5 to 28 amino acid residues. A four amino acid HCDR3 can occur in the library due to TRIM deletion, but is considered a very rare event. Another remarkable feature was the high degree of sequence homology among the selected LCDR3 sequences.

Table 2. Overview of anti-human TIMP-1 Fab

Fab	Framework + CDR 3 sequence				Monovalent K_D to human TIMP-1	IC_{50} in human protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-1	H3	FMDI, SEQ ID NO:1	?2	QSYDYQQFT, SEQ ID NO:44	65+/-13 nM*	>100 nM
MS-BW-2	H3	GFDY, SEQ ID NO:2	?2	QSYDFKTYL, SEQ ID NO:45	180+/-28 nM	>100 nM
MS-BW-3	H3	FLDI, SEQ ID NO:3	?2	QSYDFLRFS, SEQ ID NO:46	13+/-2 nM	11+/-2nM
MS-BW-25	H3	TFPIDADS, SEQ ID NO:4	?2	QSYDFINVI, SEQ ID NO:47	25+/-16nM	115+/-15 nM
MS-BW-26	H3	GHVDY, SEQ ID NO:5	?2	QSYDFVRFM, SEQ ID NO:48	~100 nM	non blocking
MS-BW-27	H3	YWRGLSFDI, SEQ ID NO:6	?2	QSYDFYKFN, SEQ ID NO:49	~74	non blocking
MS-BW-28	H3	FFDY, SEQ ID NO:7	?2	QSYDFRRFS, SEQ ID NO:50	10+/-1 nM	22+/-2nM

* In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 17

Increasing the affinity of selected anti-human TIMP-1 antibodies

[140] In order to increase the affinity of monovalent anti-human TIMP-1 Fab fragments to the sub-nanomolar range, a step-wise affinity maturation approach was applied, by optimizing CDR sequences and keeping framework regions constant.

Affinity maturation by light chain cloning

[141] The CDR3 sequences of the two antibody fragments with highest affinity (MS-BW-3 and MS-BW-28) had the remarkable feature of an unusually short four amino acid HCDR3 sequence. Furthermore, each Fab had a very similar LCDR3 sequence. This indicates that MS-BW-3 and MS-BW-28 bind to the same epitope and that this epitope might tolerate only a very small subset of CDR3 sequences. As a four amino acid HCDR3 is a very rare event in the library, it can be anticipated that in the initial library not all possible combinations of the short HCDR3 and the preferred LCDR3 are present. Therefore, it was considered that another combination of the selected HCDR3 and LCDR3 sequences might increase the affinity. For this approach, the heavy chain of MS-BW-3 and MS-BW-28 were paired with the light chains of MS-BW-1, -2, -3, -25, -26, -27, and -28 by cloning.

[142] The resulting constructs were transformed into *E. coli* and expressions/purifications in 1-liter scale were performed. Of the 12 new constructs, 10 resulted in functional Fab molecules. These were analyzed in BIAcore™ and human protease assay as summarized in Table 3. The best antibody named MS-BW-44 had a monovalent affinity of 2 nM and an IC50 of 4 nM (FIG. 7) and was thus improved by a factor of 6.5 (K_d) or 2.75 (IC_{50}).

Table 3. Overview of Fab derived from light chain cloning

Fab	Framework + CDR 3 sequence				Monovalent K_D to human TIMP-1	IC_{50}* in human protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-40	H3	FLDI, SEQ ID NO:3	?2	QSYDYQQFT, SEQ ID NO:44	~49 nM	> 100 nM
MS-BW-41	H3	FLDI, SEQ ID NO:3	?2	QSYDFKTYL, SEQ ID NO:45	~6 nM	29+/-6nM
MS-BW-43	H3	FLDI, SEQ ID NO:3	?2	QSYDFINVI, SEQ ID NO:47	~65 nM	> 100 nM
MS-BW-44	H3	FLDI, SEQ ID NO:3	?2	QSYDFVRFM, SEQ ID NO:48	2 +/- 0.4 nM*	4+/-1 nM
MS-BW-45	H3	FLDI, SEQ ID NO:3	?2	QSYDFYKFN, SEQ ID NO:49	8 +/- 5 nM	9+/-3 nM
MS-BW-46	H3	FLDI, SEQ ID NO:3	?2	QSYDFRRFS, SEQ ID NO:50	6 +/- 3 nM	4+/-0.5 nM
MS-BW-47	H3	FFDY, SEQ ID NO:7	?2	QSYDYQQFT, SEQ ID NO:44	~152 nM	> 100 nM
MS-BW-49	H3	FFDY, SEQ ID NO:7	?2	QSYDFKTYL, SEQ ID NO:45	~21 nM	> 100 nM
MS-BW-51	H3	FFDY, SEQ ID NO:7	?2	QSYDFINVI, SEQ ID NO:47	~7 nM	7+/-1 nM
MS-BW-52	H3	FFDY, SEQ ID NO:7	?2	QSYDFVRFM, SEQ ID NO:48	~11 nM	9+/-1 nM

* In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

Affinity maturation by optimizing HCDR1 and HCDR2

[143] In the HuCAL®-Fab 1 library, only the CDRs HCDR3 and LCDR3 are diversified to a high extent. Although it is known from crystallographic studies that amino acids from these two CDRs make most of the antibody antigen contacts, the residual four CDRs are also important for antigen binding. However, their contribution to the binding energy can vary from antibody to antibody. In the HuCAL®-Fab 1 library those CDRs exhibit only a limited variability due to the presence of the different master frameworks (Knappik *et al.*, 2000). In order to improve the affinity of the selected antibodies, an affinity maturation approach by randomizing HCDR1 and HCDR2 was applied. For this approach two affinity maturation libraries based on MS-BW-44 cloned into phage display vector pMORPH® 18 were created. In library 1, only HCDR2 of MS-BW-44 was diversified using "TRIM technology" as described in Virnekäs *et al.*, *Nucl. Acids. Res. 22*, 5600-07, 1994; Knappik *et al.*, *J. Mol. Biol. 296*, 57-86, 2000. In library 2, both HCDR1 and HCDR2 were diversified using the TRIM technology. In both cases, phage antibody libraries comprising 1 x 10^8 different clones were obtained. Both libraries were mixed and used as input for a modified AutoPan® procedure. In order to select antibodies having an increased affinity to human TIMP-1, solution panning using limiting amounts of biotinylated antigen and stringent washing conditions were applied. Antibody off rates were ranked by BIAcore™ using crude *E. coli* extracts of selected antibodies. Clones with slower off rate than parental clone MS-BW-44 were subjected to 1-liter scale expression and purification. Purified Fab were analyzed in BIAcore™ and human protease assay (Table 4).

Table 4. Comparison of Fab derived from HCDR1 and HCDR2 optimization with parental clone MS-BW-44

Fab	Monovalent K_D to human TIMP-1	IC_{50} in human protease assay*
MS-BW-44	2 +/- 0.4 nM	2 +/- 0.5 nM
MS-BW-44-2	0.5 +/- 0.2 nM	0.4 +/- 0.3 nM
MS-BW-44-6	0.6 +/- 0.2 nM	0.2 +/- 0.1 nM

* IC_{50} values derived from modified protease assay using decreased amounts of TIMP-1 and MMP-1 (0.4 nM each).

[144] Clone MS-BW-44-2 was derived from library 1 thus having a modified HCDR2 cassette. Its affinity measured by BIAcore™ was 0.5 nM. Clone MS-BW-44-6 was derived from library 2 having a modified HCDR 1 and HCDR 2 cassette and the affinity measured by BIAcore™ was 0.6 nM. A sequence comparison between the affinity matured antibodies and their parental clones is shown in Table 8.

Table 8: Overview and sequence comparison of affinity matured Fab fragments against human TIMP-1. Sequence changes compared to parental Fab fragments (bold) are italicized

Clone MS-BW-	VH				VL				Monov. K_D to human TIMP-1 (nM)	IC_{50} in human protease assay (nM)
	Frame-work	HCDR1 sequence (SEQ ID NO:)	HCDR2 sequence (SEQ ID NO:)	HCDR3 sequence (SEQ ID NO:)	Framework	LCDR1 sequence (SEQ ID NO:)	LCDR2 sequence (SEQ ID NO:)	LCDR3 sequence (SEQ ID NO:)		
3	VH3	**GFTFSSYAMS** (355)	**AISGSGGSTYYADSVKG** (357)	**FLDI** (3)	VL2	**TGTSSDVGGYNYVS** (363)	**DVSNRPS** (364)	**QSYDFLRFS** (47)	13 +/- 2	11 +/- 2
44	VH3	GFTFSSYAMS (355)	AISGSGGSTYYADSVKG (357)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*VRFM* (48)	2 +/- 0.4	4 +/- 1
44-6	VH3	GFTF*N*SYAMS (356)	*V*ISGNG*SN*TYYADSVKG (358)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*VRFM* (48)	0.6 +/- 0.2	0.2 +/- 0.1 *
44-2	VH3	GFTFSSYAMS (355)	*G*ISGNG*VLIF*YADSVKG (359)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*VRFM* (48)	0.5 +/- 0.2	0.4 +/- 0.3 *
44-2-4	VH3	GFTFSSYAMS (355)	*G*ISGNG*VLIF*YADSVKG (359)	*GLMDY* (360)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*VRFM* (48)	0.2 +/- 0.02	0.2 +/- 0.1 *
44-2-15	VH3	GFTFSSYAMS (355)	*G*ISGNG*VLIF*YADSVKG (359)	*WFDH* (361)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*VRFM* (48)	0.3 +/- 0.1	0.2 +/- 0.1 *
44-2-16	VH3	GFTFSSYAMS (355)	*G*ISGNG*VLIF*YADSVKG (359)	*WFDV* (362)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*VRFM* (48)	0.5 +/- 0.2	0.3 +/- 0.1 *
44-6-1	VH3	GFTF*N*SYAMS (356)	*V*ISGNG*SN*TYYADSVKG (358)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDF*IRFM* (365)	0.2 +/- 0.04	0.2 +/- 0.1 *

* IC_{50} values derived from modified protease assay using decreased amounts of TIMP-1 and MMP-1; IC_{50} of MS-BW-44 is 2 nM under these conditions

[145] When initially analyzed in the human TIMP-1/MMP-1 assay, it was not possible to distinguish a Fab with a sub-nanomolar affinity from a Fab with 1 nM affinity, most likely because the concentration of Fab required to reverse the inhibitory effect of human TIMP-1 on human MMP-1 activity by 50% was below the concentration of total TIMP-1 in the assay. When a modified assay was used with concentrations of TIMP-1 and MMP-1 decreased from 1.2 nM to 0.4 nM, it was possible to distinguish a 2 nM Fab from a sub-nanomolar Fab (Table 4, FIG. 8). Using this modified protease assay, MS-BW-44-2 and MS-BW-44-6 had IC_{50} values of 0.4 nM and 0.2 nM respectively. Parental clone MS-BW-44 had an IC_{50} of 2 nM under these conditions. Thus, by this affinity maturation approach, an affinity gain of a factor of 5 (K_d) or 5-10 (IC_{50}) was achieved.

Affinity maturation by optimizing HCDR3

[146] As mentioned above, amino acid residues in HCDR3 and LCDR3 are considered the most important for antigen binding. Taking into account that a four amino acid HCDR3 was not planned in the design of HuCAL®-Fab 1 and thus only occurs as a rare case due to a TRIM deletion, probably not all possible combinations of the four amino acids in HCDR3 were represented in the original HuCAL®-Fab 1 library. Therefore, an affinity maturation library was constructed with four and five amino acid HCDR3 maturation cassettes inserted into Fab derived from the previous maturation cycle (among them MS-BW-44-2 and MS-BW-44-6). The obtained affinity maturation library had a diversity of 1×10^8 clones, therefore theoretically covering all possible four and five amino acid HCDR3 variations. Applying very stringent panning conditions, the best antibody identified, MS-BW-44-2-4, had an affinity measured by BIAcore™ of 0.2 nM and an IC_{50} in human TIMP-1/MMP-1 assay of 0.2 nM. A sequence comparison between the affinity matured antibodies and their parental clones is shown in Table 8. The improvement factor gained by this affinity maturation approach is 2.5 with respect to the affinity and 2 with respect to the IC_{50}.

Affinity maturation by optimizing LCDR3

[147] As an alternative approach, a maturation strategy was used to further optimize the light chain CDR3 sequence. This was due to the fact that in the first maturation cycle where light chain exchange cloning between selected antibodies was applied, only a very limited subset of sequence variation had been exploited. Therefore, a maturation library was constructed in which, using TRIM technology, a diversified LCDR3 cassette was inserted into Fab derived from HCDR1 and HCDR2 optimization (among them MS-BW-44-2 and MS-BW-44-6). The best Fab identified with this maturation strategy was MS-BW-44-6-1 with an affinity measured by BIAcore™ of 0.15 nM and an IC_{50} in a human TIMP-1/MMP-1 assay of 0.2 nM. A sequence comparison between the affinity matured antibody and its parental clones is shown in Table 8. The improvement factor gained by this maturation approach is 4 with respect to affinity. A further improvement of the IC_{50} in the protease assay could not be measured due to limitations in the assay.

[148] As a result of a step-wise affinity maturation approach using four different maturation strategies, the monovalent affinity of an anti-human TIMP-1 specific Fab fragment was improved by a factor of 87 and its activity in human TIMP-1/MMP-1 assay by a factor of 55. The decision for defining the best Fab fragment has been made on the basis of K_d measurements using BIAcore™, as this method proved to be reliable for ranking antibodies with sub-nanomolar affinities, whereas the sensitivity of the human TIMP-1/MMP-1 assay was considered not suitable to rank activity of the best Fabs in the sub-nanomolar range with respect to each other.

[149] The best Fab MS-BW-44-6-1 has an affinity measured by BIAcore™ of 0.15 nM and an IC_{50} in human TIMP-1/MMP-1 assay of 0.2 nM. Compared to its parental clone, MS-BW-3, it has optimized LCDR3, HCDR1 and HCDR2 sequences.

EXAMPLE 18

Cross reactivity of selected anti-human TIMP-1 Fab with TIMP-2, TIMP-3, and TIMP-4

[150] TIMP-1 belongs to a family of closely related protease inhibitors all binding to various members of the MMP family of proteases. To date there are four human TIMP proteins described. To investigate potential cross-reactivity of antibody fragments selected against human TIMP-1 with other members of the human TIMP family, an ELISA was performed in which binding of antibody fragments to immobilized purified human TIMP-1, -2, -3 or –4 was analyzed (FIG. 10). Antibody fragments binding to immobilized human TIMP-1 showed no binding to human TIMP-2, -3, -4 above background level when compared to unrelated control protein BSA.

EXAMPLE 19

Generation of blocking antibodies against rat TIMP-1

[151] To generate blocking antibodies against rat TIMP-1, the HuCAL®-Fab 1 library was used for antibody selection (AutoPan®) on immobilized rat TIMP-1 followed by subcloning and expression of the selected Fab fragments in *E. coli*. Crude antibody-containing *E. coli* extracts were used for primary antibody characterization in ELISA (AutoScreen®). Purified Fab proteins were subjected to further characterization in ELISA, protease assays, and BIAcore™. Of the 8,450 selected clones were analyzed in AutoScreen®, 750 of them showed binding to rat TIMP-1. Sequence analysis revealed that in total 36 unique Fab clones specific for rat TIMP-1 were enriched during selection (Table 7). Their affinities were measured by BIAcore™ and were found to be in the range of 9 – 1000 nM (Table 7). When tested in the rat protease assay, all but one of them were able to block the interaction between rat TIMP-1 and rat MMP-13 (Table 7). The concentration of monovalent Fab needed to reverse the inhibitory effect of rat TIMP-1 on rat MMP-13 activity by 50% (IC_{50}) was in the range of 7 - 300 nM. The most active Fab

clones are MS-BW-14 (K_d 10 nM; IC_{50} 14 nM), MS-BW-17 (K_d 13 nM; IC_{50} 11 nM), and MS-BW-54 (K_d 9 nM; IC_{50} 7 nM).

Table 7. Overview of anti-rat TIMP-1 Fab

Fab	Framework + CDR 3 sequence				Monovalent K_D to rat TIMP-1	IC_{50}* in rat protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-5	H1A	GLYWAVYPYFDF, SEQ ID NO:8	?1	QSRDFNRGP, SEQ ID NO:51	~210 nM	non blocking
MS-BW-6	H3	LDTYYPDLFDY, SEQ ID NO:9	?1	QSYDQRKW, SEQ ID NO:52	~68 nM	~100 nM
MS-BW-7	H1A	TYYYFDS, SEQ ID NO:10	?3	QQLYGTVS, SEQ ID NO:53	~168 nM	> 300 nM
MS-BW-9	H3	YMAYMAEAIDV, SEQ ID NO:11	?1	QSYDGFKTH, SEQ ID NO:54	~256 nM	> 300 nM
MS-BW-10	H1B	LVGIVGYKPDELLYFDV, SEQ ID NO:12	?3	QSYDYSLL, SEQ ID NO:55	~200 nM	~ 30 nM
MS-BW-11	H3	YGAYFGLDY, SEQ ID NO:13	?3	QSYDFNFH, SEQ ID NO:56	~200 nM	>300 nM
MS-BW-12	H6	GYADISFDY, SEQ ID NO:14	?2	QSYDMIARYP, SEQ ID NO:57	~419 nM	>300 nM
MS-BW-13	H3	YYLLLDY, SEQ ID NO:15	?3	QSWDIHPFDV, SEQ ID NO:58	~939 nM	not tested
MS-BW-14	H1A	WSDQSYHYYWHPYFDV, SEQ ID NO:16	?1	QSWDLEPY, SEQ ID NO:59	10 +/- 5 nM	14+/-3 nM
MS-BW-15	H3	LIGYFDL, SEQ ID NO:17	?2	QSYDVLDSE, SEQ ID NO:60	~80 nM	~ 200 nM
MS-BW-17	H5	LTNYFDSIYYDH, SEQ ID NO:18	?2	QSYDPSHPSK, SEQ ID NO:61	13 +/- 3 nM	11+/-3 nM
MS-BW-18	H5	LVGGGYDLMFDS, SEQ ID NO:19	?2	QSYDDMQF, SEQ ID NO:62	~153 nM	> 300 nM
MS-BW-19	H5	YVTYGYDDYHFDY, SEQ ID NO:20	?2	QSWDINHAI, SEQ ID NO:63	~187 nM	> 300 nM
MS-BW-20	H1A	SGYLDY, SEQ ID NO:21	?2	QSYDYYDYG, SEQ ID NO:64	~70 nM	> 300 nM

MS-BW-21	H1A	YIGYTNVMDIRPGYFLDY, SEQ ID NO:22	?3	QQANDFPI, SEQ ID NO:65	36 +/- 2 nM	67+/-5nM
MS-BW-22	H5	FRAYGDDFYFDV, SEQ ID NO:23	?2	QSWDNLKMPV, SEQ ID NO:66	35 nM	65+/-11 nM
MS-BW-23	H1B	JMWSDYGQLVKGGDI, SEQ ID NO:24	?2	QSYDVFPINR, SEQ ID NO:67	~207 nM	> 300 nM
MS-BW-24	H5	YYVTDTAYFDY, SEQ ID NO:25	?2	QSDLYFP, SEQ ID NO:68	23 nM	20+/-1 nM
MS-BW-29	H5	HDFDGSIFMDF, SEQ ID NO:26	? 2	QSYDVTPR, SEQ ID NO:69	~214 nM	>100 nM
MS-BW-30	H5	YAGHQYEFFFDF, SEQ ID NO:27	? 3	QSRDPVGFP, SEQ ID NO:70	~36 nM	>100 nM
MS-BW-31	H5	LYADADIYFDY, SEQ ID NO:28	? 2	QSYDLSPR, SEQ ID NO:71	~13 +/- 9 nM	>100 nM
MS-BW-32	H1A	TKYVGSEDV, SEQ ID NO:29	? 2	QSYDFSHYFF, SEQ ID NO:72	~92 nM	> 100 nM
MS-BW-36	H5	YRYPHMFDF, SEQ ID NO:30	? 3	QSYDLRYSH, SEQ ID NO:73	~42 nM	~75 nM
MS-BW-37	H5	LFAGLELYFDY, SEQ ID NO:31	? 2	QSYDLRNR, SEQ ID NO:74	10 +/- 9 nM	>100 nM
MS-BW-38	H3	GGFFNMDY, SEQ ID NO:32	? 2	QSYDFTYGS, SEQ ID NO:75	~353 nM	>300 nM
MS-BW-39	H1A	GYIPYHLFDY, SEQ ID NO:33	?3	QQFNDSPY, SEQ ID NO:76	~108 nM	>100 nM
MS-BW-54	H5	YYGFEYDLLFDN, SEQ ID NO:34	? 2	QSYDISGYP, SEQ ID NO:77	9 +/- 1 nM	7 nM
MS-BW-55	H1B	ITYIGYDF, SEQ ID NO:35	? 2	QSRDLYYVYY, SEQ ID NO:78	~23 nM	~ 100 nM
MS-BW-56	H1A	QEWYMDY, SEQ ID NO:36	? 3	QSYDRSMW, SEQ ID NO:79	~170 nM	> 100 nM
MS-BW-57	H5	LYPEDLIYFDY, SEQ ID NO:37	? 2	QSWDVQTDK, SEQ ID NO:80	~39 nM	~60 nM
MS-BW-58	H6	WMTPPGHYYGYTFDV, SEQ ID NO:38	? 3	QSWDPSHYY, SEQ ID NO:81	~138 nM	not tested
MS-BW-59	H5	LRVHDYAMYFDL, SEQ ID NO:39	? 2	QSYDIMPER, SEQ ID NO:82	~15 nM	30 +/- 5nM

MS-BW-60	H5	FVSYNGSVPYFDY, SEQ ID NO:40	? 2	QSMDFRLMH, SEQ ID NO:83	~30 nM	> 100 nM
MS-BW-61	H5	IIGDYVIFFDV, SEQ ID NO:41	? 2	QSFDMIHPY, SEQ ID NO:84	~51 nM	> 100 nM
MS-BW-62	H5	LFTYPFLYFDV, SEQ ID NO:42	? 2	QSDFPVM, SEQ ID NO:85	~36 nM	19 +/- 2
MS-BW-63	H5	ILTGHVLLFDY, SEQ ID NO:43	? 2	QSDNPYL, SEQ ID NO:86	~14 nM	20 +/- 1nM

* In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 20

Increasing the affinity of selected anti-rat TIMP-1 antibodies

[152] Affinity maturation was applied to increase the affinity of monovalent anti-rat TIMP-1 Fab fragments to the sub-nanomolar range. No clear sequence homology could be identified among the light chain CDR3 sequences of the selected antibody fragments, indicating that an optimal light chain CDR3 sequence was probably not present or had not been selected from the original HuCAL®-Fab 1 library. We therefore started with modification of LCDR3 to increase the affinity of Fabs.

[153] Two affinity maturation libraries based on MS-BW-14, -17, and -54 cloned into phage display vector pMORPH® 18 were created. In library 1, only LCDR3 was diversified using TRIM technology, as described in Virnekäs *et al., Nucl. Acids. Res. 22*, 5600-07, 1994; Knappik *et al., J. Mol. Biol. 296*, 57-86, 2000. In library 2, LCDR1, LCDR2, and LCDR3 were diversified simultaneously using the TRIM technology, while the connecting framework regions were kept constant. In both cases, phage antibody libraries comprising 3 x 10^8 different clones were obtained. Both libraries were mixed and used as input for a modified AutoPan® procedure. To select antibodies having an increased affinity to rat TIMP-1, solution panning using limiting amounts of biotinylated antigen and stringent washing conditions were applied.

[154] Antibody-off-rates were ranked by BIAcore™ using crude *E. coli* extracts. Clones with slower off rate than parental clones MS-BW-14, -17, or -54 were subjected to expression and purification in 1-liter scale. Purified Fab were analyzed in BIAcore™ and rat protease assays (Table 6). MS-BW-17-1 (K_d 0.8 nM, IC_{50} 1.6 nM), MS-BW-17-2 (K_d 1.3 nM, IC_{50} 1.1 nM), and MS-BW-17-3 (K_d 1.9 nM, IC_{50} 3 nM) were derived from affinity maturation library 1 having an optimized LCDR3 sequence, whereas MS-BW-

54-1 (K_d 2 nM, IC_{50} 3 nM) was derived from affinity maturation library 2 having an optimized LCDR1, -2, and -3 sequence (Table 9).

Table 9. Overview and sequence comparison of affinity matured Fab fragments against rat TIMP-1. Sequence changes compared to parental Fab fragments (bold) are italicized.

Clone (MS-BW-)	VH				VL				Monov. K_D to rat TIMP-1 (nM)	IC_{50} in rat protease assay (nM)
	Frame-work	HCDR1 sequence (SEQ ID NO:)	HCDR2 sequence (SEQ ID NO:)	HCDR3 sequence (SEQ ID NO:)	Frame-work	LCDR1 sequence (SEQ ID NO:)	LCDR2 sequence (SEQ ID NO:)	LCDR3 sequence (SEQ ID NO:)		
14	VH1A	**GGTFSSYAIS** (366)	**GIIPIFGTANYAQKFQG** (368)	**WSDQSYHYYWHPYFDV** (370)	VL1	**SGSSSNIGSNYVS** (371)	**LMIYDNNQRPS** (373)	**QSWDLEPY** (59)	10 +/- 5	14 +/- 3
17	VH5	**GYSFTSYWIG** (367)	**IIYPGDSDTRYSPSFQG** (369)	**LTNYFDSIYYDH** (18)	VL2	**TGTSSDVGGYNYVS** (363)	**LMIYDVSNRPS** (374)	**QSYDPSHPSK** (61)	13 +/- 3	11 +/- 3
54	VH5	**GYSFTSYWIG** (367)	**IIYPGDSDTRYSPSFQG** (369)	**YYGFEYDLLFDN** (34)	VL2	**TGTSSDVGGYNYVS** (363)	**LMIYDVSNRPS** (374)	**QSYDISGYP** (77)	9 +/-1	7
17-1	VH5	GYSFTSYWIG (367)	IIYPGDSDTRYSPSFQG (369)	LTNYFDSIYYDH (18)	VL2	TGTSSDVGGYNYVS (363)	LMIYDVSNRPS (374)	QA*FDVAPNG* K (376)	0.8	1.6
17-2	VH5	GYSFTSYWIG (367)	IIYPGDSDTRYSPSFQG (369)	LTNYFDSIYYDH (18)	VL2	TGTSSDVGGYNYVS (363)	LMIYDVSNRPS (374)	QA*FAVMPNV* *E* (377)	1.3	1.1
17-3	VH5	GYSFTSYWIG (367)	IIYPGDSDTRYSPSFQG (369)	LTNYFDSIYYDH (18)	VL2	TGTSSDVGGYNYVS (363)	LMIYDVSNRPS (374)	QS*FTVS* *PGA* *D* (378)	1.9	3
54-1	VH5	GYSFTSYWIG (367)	IIYPGDSDTRYSPSFQG (369)	YYGFEYDLLFDN (34)	VL2	TGTSSD*L*GGYNYVS (372)	LMIY*AG*[illegible]RPS (375)	QAYDSSGYP (379)	2	3

[155] The improvement gained by these different one-step maturation strategies was up to a factor of 16.3 with regard to affinity and 10 with regard to functional activity in the protease assay.

EXAMPLE 21

Conversion of anti-TIMP-1 Fab fragments into human IgG_1 molecules for use in the rat model of chronic carbon tetrachloride-induced liver fibrosis

[156] Anti-TIMP-1 Fab fragments were converted into human IgG1 molecules to create antibody molecules with prolonged *in vivo* half-lives for the use in the rat model of chronic carbon tetrachloride-induced liver fibrosis. This was done by cloning the heavy and light chain variable regions of the Fab into two separate vectors for mammalian IgG_1 expression (Krebs *et al.*, 2001)

[157] Anti-rat TIMP-1 clone MS-BW-14 was chosen for the first *in vivo* study, and IgG_1 protein was produced by transient expression. Anti-human TIMP-1 clone MS-BW-3 was selected as a negative control IgG_1 and was also produced by transient expression. Purified IgG_1 proteins MS-BW-14 and MS-BW-3 were subjected to quality control in BIAcore™ and rat TIMP-1/rat MMP-13 assays. Bivalent affinity for rat TIMP-1 measured in BIAcore™ (chip density 500 RU, fitting model for bivalent analyte) is 0.2 nM for MS-BW-14, compared to 13 nM for the corresponding monovalent Fab fragment. This increase in affinity for the IgG_1 is due to the avidity effects caused by binding of bivalent IgG_1 to immobilized rat TIMP-1 protein on the BIAcore™ chip. As expected, the negative control IgG_1 MS-BW-3 showed no binding to rat TIMP-1 but bound to human TIMP-1 with a bivalent affinity of approximately 0.4 nM.

[158] FIG. 12 shows the activity of MS-BW-14 Fab and IgG_1 and MS-BW-3 IgG_1 in a rat TIMP-1/rat MMP-13 assay. The IC_{50} of MS-BW-14 Fab and IgG_1 are nearly identical. The avidity effect seen in BIAcore™ does not occur in this assay because, in contrast to

the BIAcore™ experiment, this assay is based on a monovalent interaction in solution between TIMP-1 and the IgG_1. As expected, MS-BW-3 has no effect on rat TIMP-1 binding to rat MMP-13 and thus is a suitable negative control for a rat *in vivo* study.

[159] Affinity matured clone MS-BW-17-1 was then converted from a monovalent Fab fragment to a bivalent IgG_1. Protein was produced by stable transfection. Purified protein was subjected to quality control in BIAcore™ and rat TIMP-1/rat MMP-13 assays (FIG. 13). In BIAcore™ an increased bivalent affinity (avidity) of 0.04 nM for IgG_1 compared to 0.8 nM for monovalent Fab fragment was seen, whereas the activity in the rat TIMP-1/rat MMP-13 assay was comparable for IgG_1 and Fab as expected.

EXAMPLE 22

Cross-reactivity of anti-rat TIMP-1 IgG_1 MS-BW-17-1 with mouse TIMP-1

[160] Species cross-reactivity of MS-BW-17-1 IgG_1 and Fab with mouse TIMP-1 was determined by BIAcore™ to investigate the feasibility of alternative *in vivo* models that use mice instead of rats. Although MS-BW-17-1 clearly bound to mouse TIMP-1 immobilized to the chip surface, the affinity of both Fab (180 nM) and IgG_1 (9 nM) was 225-fold weaker than the affinity to rat TIMP-1. As the interaction between mouse TIMP-1 and BW-17-1 IgG_1 in serum is most likely monovalent, the affinity of BW-17-1 Fab probably reflects the "real" affinity of this interaction. Therefore, the Fab affinity value should be considered when calculating the feasibility of using BW-17-1 IgG_1 in a mouse *in vivo* study.

EXAMPLE 23

Effect of Timp-1 antibody on the development of bleomycin-induced pulmonary fibrosis

[161] The following example demonstrates the ability of a human anti-rat Timp-1 antibody (BW17.1) to prevent fibrotic collagen deposition in a bleomycin-induced rat lung fibrosis model.

[162] Male Lewis rats (6 weeks of age) received a single intratracheal challenge with bleomycin (0.3 mg/rat, in saline) or vehicle (saline) on day 0. Fourteen days later, animals were euthanized, the lung excised, fixed, and processed for evaluation of lung fibrosis. Lung tissue sections were cut, and quantitative assessment by image analysis of lung collagen in lung tissue sections stained with Mason Trichrome stain performed.

[163] Antibody administration: A 20 mg/kg dose of human ant-rat TIMP-1 antibody or control human antibody (IgG) was administered subcutaneously on day -1. Subsequently, a 10mg/kg dose of human ant-rat TIMP-1 antibody or control human antibody (IgG) was administered s.c. on days 2, 5, 8, and 11. The following five groups of animals were studied: Saline i.t. challenge + antibody vehicle (PBS); Saline i.t. challenge + TIMP-1 antibody; Bleomycin i.t. challenge + TIMP-1 antibody; Bleomycin i.t. challenge + antibody vehicle (PBS); Bleomycin i.t. challenge + control antibody.

[164] FIG. 14 shows the effect of the inhibitory effect of TIMP-1 antibody on bleomycin-induced lung fibrotic collagen.

EXAMPLE 24

Effect of BW-14 anti-TIMP-1 antibody in a rat model with CCl_4-induced liver fibrosis

[165] Carbon tetrachloride (CCl_4) was used to induce liver fibrosis as described in Example 9. A single intravenous dose of 3 mg/kg BW-14 or control antibody BW-3, respectively,

was administered on day 19. At this time, total liver collagen (hydroxyproline determined according to Prockop and Udenfried) is already significantly increased by CCl_4, and fibrotic collagen rapidly accumulates during the following weeks. The rats were sacrificed on day 28. The treatment groups were: no CCl_4 + control antibody BW 3 (n=10 rats), CCl_4 + control antibody BW 3 (n=20 rats), and CCl_4 + BW 14 (n=20 rats).

[166] The effect of control vs. TIMP-1 antibody as reflected in morphometric measurements of fibrous collagen (Sirius Red stained area as percentage of the total field) is shown in FIG. 15. Comparison of both control antibody treated groups shows that CCl_4 caused an approximately three-fold increase in collagen area. BW-14 antibody treatment reduced the pathological collagen increment by 26%. The lower fibrous collagen value of the CCl_4 + BW-14 group compared to the CCl_4 + BW-3 group was statistically significant ($p < 0.05$, Kolmogorow-Smirnow test).

REFERENCES

[167] Ausubel *et al.* (1998) Current Protocols in Molecular Biology. Wiley, New York, USA.

[168] Better *et al.*, (1988) Escherichia coli secretion of an active chimeric antibody fragment. Science 240, 1041.

[169] Bruggeman *et al.*, (1996) Phage antibodies against an unstable hapten: oxygen sensitive reduced flavin. FEBS Lett. 388, 242.

[170] Butler *et al.*, (1999) Human tissue inhibitor of metalloproteinases 3 interacts with both the N- and C-terminal domains of gelatinases A and B. Regulation by polyanions. J Biol Chem. 274, 10846.

[171] Gomis-Ruth *et al.*, (1996). Mechanism of inhibition of the human matrix metalloproteinase stromelysin-1 by TIMP-1. Nature. 389, 77.

[172] Griffiths, A.D. and Duncan, A.R. (1998) Strategies for selection of antibodies by phage display. Curr. Opin. Biotechnol. 9, 102.

[173] Hoogenboom, H.R. and Winter, G. (1992). By-passing immunisation. Human antibodies from synthetic repertoires of germline VH gene segments rearranged *in vitro*. J. Mol. Biol. 227, 381.

[174] Iredale *et al.*, (1996) Tissue inhibitor of metalloproteinase-1 messenger RNA expression is enhanced relative to interstitial collagenase messenger RNA in experimental liver injury and fibrosis. Hepatology. 24, 176.

[175] Knappik *et al.*, (2000) Fully synthetic human combinatorial antibody libraries (HuCAL) based on modular consensus frameworks and CDRs diversified with trinucleotides. J. Mol. Biol. 296, 55.

[176] Krebs *et al.*, (2001) High-throughput generation and engineering of recombinant human antibodies. J Immunol Methods. 254, 67.

[177] Lowman, H.B. (1997) Bacteriophage display and discovery of peptide leads for drug development. Annu. Rev. Biophys. Biomol. Struct. 26, 401.

[178] McCafferty *et al.*, (1990) Phage antibodies: filamentous phage displaying antibody variable domains. Nature 348, 552.

[179] Meng *et al.*, (1999) Residue 2 of TIMP-1 is a major determinant of affinity and specificity for matrix metalloproteinases but effects of substitutions do not correlate with those of the corresponding P1' residue of substrate. J Biol Chem. 274, 10184.

[180] Meulemans *et al.*, (1994) Selection of phage-displayed antibodies specific for a cytoskeletal antigen by competitive elution with a monoclonal antibody. J. Mol. Biol. 244, 353.

[181] Miyazaki *et al.*, (1999) Changes in the specificity of antibodies by site-specific mutagenesis followed by random mutagenesis. Protein Eng. 12, 407.

[182] Sheets *et al.*, (1998) Efficient construction of a large nonimmune phage antibody library: The production of high-affinity human single-chain antibodies to protein antigens. Proc. Natl. Acad. Sci. U.S.A. 95, 6157.

[183] Skerra, A. and Plückthun, A. (1988) Assembly of a functional immunoglobulin Fv fragment in Escherichia coli. Science 240, 1038.

[184] Smith, G.P. (1985) Filamentous fusion phage: novel expression vectors that display cloned antigens on the virion surface. Science 228, 1315.

[185] Smith, G.P. and Petrenko, V.A. (1997) Phage display. Chem. Rev. 97, 391.

[186] Stausbøl-Grøn *et al.*(1996) A model phage display subtraction method with potential for analysis of differential gene expression. FEBS Lett. 391, 71.

[187] Virnekäs *et al.* (1994) Trinucleotide phosphoramidites: ideal reagents for the synthesis of mixed oligonucleotides for random mutagenesis. Nucl. Acids Res. 22, 5600.

CLAIMS

1. A purified preparation of a human antibody, wherein the antibody:

binds to a tissue inhibitor of metalloprotease-1 (TIMP-1); and

neutralizes a matrix metalloprotease (MMP)-inhibiting activity of the TIMP-1.

2. The preparation of claim 1 wherein the MMP is human MMP-1.

3. The preparation of claim 2 wherein the MMP is rat MMP-13.

4. The preparation of claim 1 wherein the TIMP-1 is a human TIMP-1.

5. The preparation of claim 4 wherein the antibody binds to the human TIMP-1 with a K_d selected from the group consisting of about 0.1 nM to about 10 μM, about 2 nM to about 1 μM, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 0.2 nM to about 13 nM, about 0.2 nM to about 0.5 nM, about 2 nM to about 13 nM, and about 0.5 nM to about 2 nM.

6. The preparation of claim 4 wherein the antibody binds to the human TIMP-1 with a K_d selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.5 M, about 0.6 nM, about 2 nM, about 7 nM, about 10 nM, about 11 nM, and about 13 nM.

7. The preparation of claim 4 wherein the antibody neutralizes the MMP-inhibiting activity of the human TIMP-1 with an IC_{50} selected from the group consisting of about .1 nM to about 200 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 0.2 nM to about 11 nM, about 0.2 nM to about 4 nM, and about 4 nM to about 11 nM.

8. The preparation of claim 4 wherein the antibody neutralizes the MMP-inhibiting activity of the human TIMP-1 with an IC_{50} selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.4 nM, about 4 nM, about 7 nM, about 9 nM, and about 11 nM.

9. The preparation of claim 4 wherein the K_d for binding to human TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the human TIMP-1 are approximately equal.

10. The preparation of claim 1 wherein the TIMP-1 is a rat TIMP-1.

11. The preparation of claim 10 wherein the antibody binds to the rat TIMP-1 with a K_d selected from the group consisting of about 0.1 nM to about 10 μM, about 2 nM to about 1 μM, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 1.3 nM to about 13 nM, about 1.8 nM to about 10 nM, about 2 nM to about 9 nM, about 1.3 nM to about 9 nM, and about 2 nM to about 10 nM.

12. The preparation of claim 10 wherein the antibody binds to the rat TIMP-1 with a K_d selected from the group consisting of about 0.8 nM, about 1 nM, about 1.3 nM, about 1.9 nM, about 2 nM, about 3 nM, about 9 nM, about 10 nM, about 13 nM, about 14 nM, and about 15 nM.

13. The preparation of claim 10 wherein the antibody neutralizes the rat TIMP-1 activity with an IC_{50} selected from the group consisting of about .1 nM to about 300 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 1.1 nM to about 14 nM, about 1.6 nM to about 11 nM, about 3

nM to about 7 nM, about 1.1 nM to about 7 nM, about 1.1 nM to about 11 nM, about 3 nM to about 11 nM, and about 3 nM to about 14 nM.

14. The preparation of claim 10 wherein the antibody neutralizes the rat TIMP-1 activity with an IC_{50} selected from the group consisting of about 1.1 nM, about 1.6 nM, about 3 nM, about 7 nM, about 11 nM, about 14 nM, about 19 nM, about 20 nM, about 30 nM, and about 100 nM.

15. The preparation of claim 10 wherein the K_d for binding to rat TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the rat TIMP-1 are approximately equal.

16. A purified preparation of a human antibody which comprises a VHCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360.

17. A purified preparation of a human antibody which comprises a VLCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379.

18. A purified preparation of a human antibody which comprises a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10

and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

19. A purified preparation of a human antibody comprising a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID

NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

20. The purified preparation of claim 19 wherein the human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.

21. The purified preparation of claim 19 wherein the human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

22. A purified preparation of a human antibody which comprises a heavy chain and a light chain amino acid pair selected from the group consisting of SEQ ID NOS:140 and 97, SEQ ID NOS:141 and 98, SEQ ID NOS:142 and 99, SEQ ID NOS:143 and 100, SEQ ID NOS:144 and 101, SEQ ID NOS:145 and 102, SEQ ID NOS:146 and 103, SEQ ID NOS:142 and 97, SEQ ID NOS:142 and 98, SEQ ID NOS:142 and 100, SEQ ID NOS:142 and 101,

SEQ ID NOS:142 and 102, SEQ ID NOS:142 and 103, SEQ ID NOS:146 and 97, SEQ ID NOS:146 and 98, SEQ ID NO:146 and 100, SEQ ID NOS:146 and 101, SEQ ID NOS:148 and 104, SEQ ID NOS:148 and 105, SEQ ID NOS:149 and 106, SEQ ID NOS:150 and 107, SEQ ID NOS:151 and 108, SEQ ID NOS:152 and 109, SEQ ID NOS:153 and 110, SEQ ID NOS:154 and 111, SEQ ID NOS:155 and 112, SEQ ID NOS:156 and 113, SEQ ID NOS:157 and 114, SEQ ID NOS:158 and 115, SEQ ID NOS:159 and 116, SEQ ID NOS:160 and 117, SEQ ID NOS:161 and 118, SEQ ID NOS:162 and 119, SEQ ID NOS:163 and 120, SEQ ID NOS:164 and 121, SEQ ID NOS:165 and 122, SEQ ID NOS:166 and 123, SEQ ID NOS:167 and 124, SEQ ID NOS:168 and 125, SEQ ID NOS:169 and 126, SEQ ID NOS:170 and 127, SEQ ID NOS:171 and 128, SEQ ID NOS:172 and 129, SEQ ID NOS:173 and 130, SEQ ID NOS:174 and 131, SEQ ID NOS:175 and 132, SEQ ID NOS:176 and 133, SEQ ID NOS:177 and 134, SEQ ID NOS:178 and 135, SEQ ID NOS:179 and 136, SEQ ID NOS:180 and 137, SEQ ID NOS:181 and 138, and SEQ ID NOS:182 and 139.

23. A pharmaceutical composition comprising:

a human antibody which (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1; and

a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23 wherein the MMP is human MMP-1.

25. The pharmaceutical composition of claim 23 wherein the MMP is rat MMP-13.

26. The pharmaceutical composition of claim 23 wherein the TIMP-1 is a human TIMP-1.

27. The pharmaceutical composition of claim 23 wherein the TIMP-1 is a rat TIMP-1.

28. The pharmaceutical composition of claim 23 wherein a K_d for binding to the TIMP-1 and an IC_{50} for neutralizing the MMP-1-inhibiting activity of the TIMP-1 are approximately equal.

29. A purified polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

30. The purified polynucleotide of claim 31 wherein the VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.

31. A purified polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

32. The purified polynucleotide of claim 31 wherein the VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.

33. The purified polynucleotide of claim 31 wherein the human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.

34. The purified polynucleotide of claim 33 wherein the heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.

35. The purified polynucleotide of claim 33 wherein the human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

36. The purified polynucleotide of claim 35 wherein the light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.

37. An expression vector comprising the polynucleotide of claim 29.

38. An expression vector comprising the polynucleotide of claim 30.

39. An expression vector comprising the polynucleotide of claim 31.

40. An expression vector comprising the polynucleotide of claim 32.

41. An expression vector comprising the polynucleotide of claim 33.

42. An expression vector comprising the polynucleotide of claim 34.

43. An expression vector comprising the polynucleotide of claim 35.

44. An expression vector comprising the polynucleotide of claim 36.

45. A host cell comprising the expression vector of claim 37.

46. A host cell comprising the expression vector of claim 38.

47. A host cell comprising the expression vector of claim 39.

48. A host cell comprising the expression vector of claim 40.

49. A host cell comprising the expression vector of claim 41.

50. A host cell comprising the expression vector of claim 42.

51. A host cell comprising the expression vector of claim 43.

52. A host cell comprising the expression vector of claim 44.

53. A method of making a human antibody, comprising the steps of:

culturing the host cell of claim 45 under conditions whereby the antibody is expressed; and

purifying the human antibody from the host cell culture.

54. The method of claim 55 wherein the expression vector comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOS:183-357.

55. A method of decreasing an MMP-inhibiting activity of a TIMP-1, comprising the step of:

contacting the TIMP-1 with a human antibody that binds to the TIMP-1, whereby the MMP-inhibiting activity of the TIMP-1 is decreased relative to MMP-inhibiting activity of the TIMP-1 in the absence of the antibody.

56. The method of claim 55 wherein the MMP is human MMP-1.

57. The method of claim 55 wherein the MMP is rat MMP-13.

58. The method of claim 55 wherein the TIMP-1 is a human TIMP-1.

59. The method of claim 55 wherein the TIMP-1 is a rat TIMP-1.

60. The method of claim 55 wherein the step of contacting is carried out in a cell-free system.

61. The method of claim 55 wherein the step of contacting is carried out in a cell culture system.

62. The method of claim 55 wherein the step of contacting is carried out *in vivo*.

63. The method of claim 55 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

64. A method of ameliorating symptoms of a disorder in which TIMP-1 is elevated, comprising the step of:

administering to a patient having the disorder an effective amount of a human antibody which neutralizes an MMP-inhibiting activity of the TIMP-1, whereby symptoms of the disorder are ameliorated.

65. The method of claim 64 wherein the MMP is human MMP-1.

66. The method of claim 64 wherein the MMP is rat MMP-13.

67. The method of claim 64 wherein the disorder is selected from the group consisting of liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, and colon cancer.

68. The method of claim 64 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71,

SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

69. A method of detecting a TIMP-1 in a test preparation, comprising the steps of:.

contacting the test preparation with a human antibody that specifically binds to the TIMP-1; and

assaying the test preparation for the presence of an antibody-TIMP-1 complex.

70. The method of claim 69 wherein the antibody comprises a detectable label.

71. The method of claim 69 wherein the antibody is bound to a solid support.

72. The method of claim 69 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID

NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, and SEQ ID NOS:43 and 86.

73. A method to aid in diagnosing a disorder in which a TIMP-1 level is elevated, comprising the steps of:

contacting a sample from a patient suspected of having the disorder with a human antibody that binds to TIMP-1; and

assaying for the presence of an antibody-TIMP-1 complex, whereby detection of an amount of the complex which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.

74. The method of claim 73 wherein the antibody comprises a detectable label.

75. The method of claim 73 wherein the antibody is bound to a solid support.

76. The method of claim 73 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID

NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

77. The method of claim 73 wherein the sample is obtained from a tissue selected from the group consisting of colon, liver, heart, kidney, prostate, serum, and lung.

78. The method of claim 73 wherein the disorder is selected from the group consisting of liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute cardiac syndrome,

lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, lung cancer, colon cancer, and idiopathic pulmonary fibrosis.

Sequence Summary HuCAL Libraries scFv1, scFv2, scFv3 and Fab1

VL

Position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	a	b	c	d	e	f	31	32	33	34
	Framework 1																							CDR 1																
	EcoRV						BanII																PstI																	
VLκ1	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	G	I	S	-	-	-	-	-	-	S	Y	L	A
VLκ2	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	L	L	H	S	-	N	G	Y	N	Y	L	D
VLκ3	D	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	R	A	S	Q	S	V	S	S	-	-	-	-	-	S	Y	L	A
VLκ4	D	I	V	M	T	Q	S	P	D	S	L	A	V	S	L	G	E	R	A	T	I	N	C	R	S	S	Q	S	V	L	Y	S	S	N	N	K	N	Y	L	A
VLλ1	D	I	V	L	T	Q	P	P	-	S	V	S	G	A	P	G	Q	R	V	T	I	S	C	S	G	S	S	S	N	I	G	S	-	-	-	-	N	Y	V	S
VLλ2	D	I	A	L	T	Q	P	A	-	S	V	S	G	S	P	G	Q	S	I	T	I	S	C	T	G	T	S	S	D	V	G	G	Y	-	-	-	N	Y	V	S
VLλ3	D	I	E	L	T	Q	P	P	-	S	V	S	V	A	P	G	Q	T	A	R	I	S	C	S	G	D	A	L	G	D	-	-	-	-	-	-	K	Y	A	S
	EcoRV														SexAI							BssSI																		

VH

Position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	a	b	32	33	34	35	36	37	38
	Framework 1																									CDR 1														
			MfeI																						BspEI															
VH1A	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	G	T	F	S	S	-	-	Y	A	I	S	W	V	R
VH1B	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	S	-	-	Y	Y	M	H	W	V	R
VH2	Q	V	Q	L	K	E	S	G	P	A	L	V	K	P	T	Q	T	L	T	L	T	C	T	F	S	G	F	S	L	S	T	S	G	V	G	V	G	W	I	R
VH3	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	S	S	-	-	Y	A	M	S	W	V	R
VH4	Q	V	Q	L	Q	E	S	G	P	G	L	V	K	P	S	E	T	L	S	L	T	C	T	V	S	G	G	S	I	S	S	-	-	Y	Y	W	S	W	I	R
VH5	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	E	S	L	K	I	S	C	K	G	S	G	Y	S	F	T	S	-	-	Y	W	I	G	W	V	R
VH6	Q	V	Q	L	Q	Q	S	G	P	G	L	V	K	P	S	Q	T	L	S	L	T	C	A	I	S	G	D	S	V	S	S	N	S	A	A	W	N	W	I	R

FIG. 1

Framework 2															CDR 2							Framework 3																						
					4										5										6										7									
5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
KpnI					SexAI							AseI										SanDI									BamHI													
W	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	A	A	S	S	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q
W	Y	L	Q	K	P	G	Q	S	P	Q	L	L	I	Y	L	G	S	N	R	A	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V	E
W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	G	A	S	S	R	A	T	G	V	P	A	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	E
W	Y	Q	Q	K	P	G	Q	P	P	K	L	L	I	Y	W	A	S	T	R	E	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q
W	Y	Q	Q	L	P	G	T	A	P	K	L	L	I	Y	D	N	N	Q	R	P	S	G	V	P	D	R	F	S	G	S	K	S	G	T	S	A	S	L	A	I	T	G	L	Q
W	Y	Q	Q	H	P	G	K	A	P	K	L	M	I	Y	D	V	S	N	R	P	S	G	V	S	N	R	F	S	G	S	K	S	G	N	T	A	S	L	T	I	S	G	L	Q
W	Y	Q	Q	K	P	G	Q	A	P	V	L	V	I	Y	D	D	S	D	R	P	S	G	I	P	E	R	F	S	G	S	N	S	G	N	T	A	T	L	T	I	S	G	T	Q
KpnI					XmaI			BbeI												Bsu36I										BamHI														

Framework 2											CDR 2																		Fra															
	4										5												6										7											8
9	0	1	2	3	4	5	6	7	8	9	0	1	2	a	b	c	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0
	BstXI					XhoI																									BstEII							NspV						
Q	A	P	G	Q	G	L	E	W	M	G	G	I	I	P			I	F	G	T	A	N	Y	A	Q	K	F	Q	G	R	V	T	I	T	A	D	E	S	T	S	T	A	Y	M
Q	A	P	G	Q	G	L	E	W	M	G	W	I	N	P			N	S	G	G	T	N	Y	A	Q	K	F	Q	G	R	V	T	M	T	R	D	T	S	I	S	T	A	Y	M
Q	P	P	G	K	A	L	E	W	L	A	L	I	D				W	D	D	D	K	Y	Y	S	T	S	L	K	T	R	L	T	I	S	K	D	T	S	K	N	Q	V	V	L
Q	A	P	G	K	G	L	E	W	V	S	A	I	S	G			S	G	G	S	T	Y	Y	A	D	S	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L
Q	P	P	G	K	G	L	E	W	I	G	Y	I	Y				Y	S	G	S	T	N	Y	N	P	S	L	K	S	R	V	T	I	S	V	D	T	S	K	N	Q	F	S	L
Q	M	P	G	K	G	L	E	W	M	G	I	I	Y	P			G	D	S	D	T	R	Y	S	P	S	F	Q	G	Q	V	T	I	S	A	D	K	S	I	S	T	A	Y	L
Q	S	P	G	R	G	L	E	W	L	G	R	T	Y	Y	R		S	K	W	Y	N	D	Y	A	V	S	V	K	S	R	I	T	I	N	P	D	T	S	K	N	Q	F	S	L

FIG. 1, Cont.

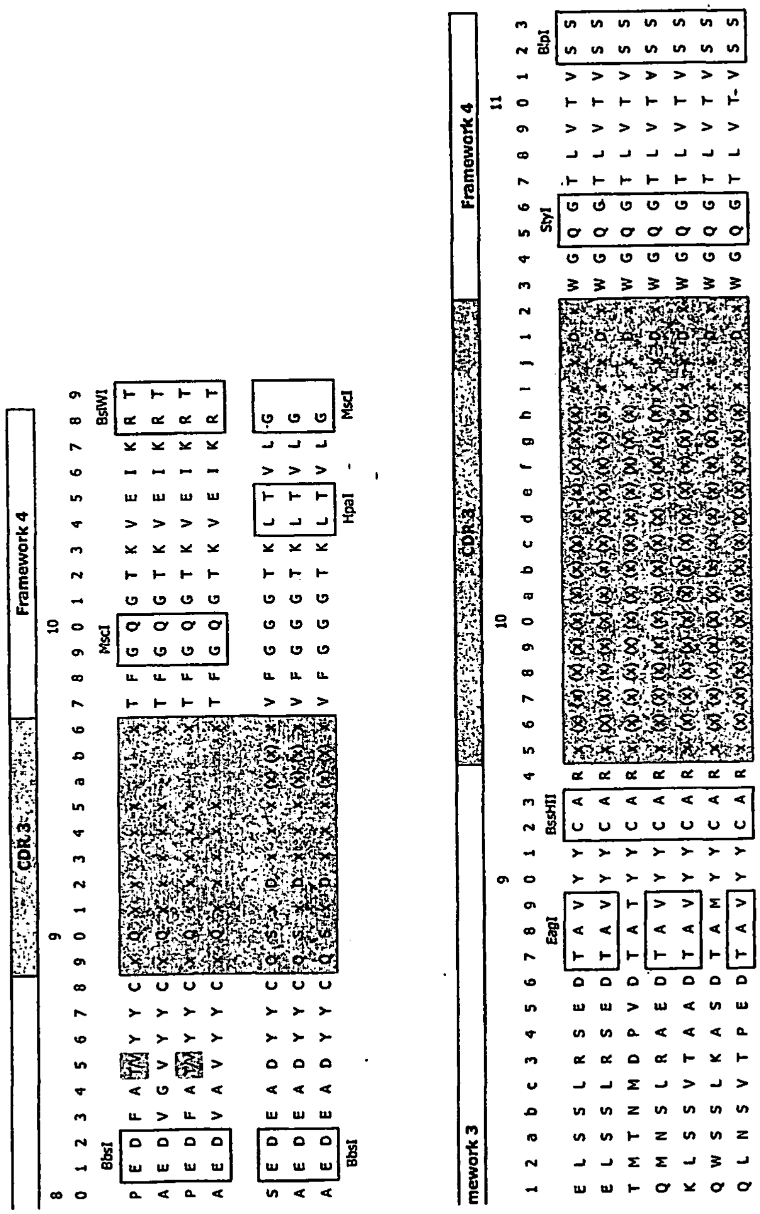

FIG. 1, cont.

Sequence Summary HuCAL Libraries scFv1, scFv2, scFv3 and Fab1

VL

Framework 1 (positions 1–23) | CDR 1 (positions 24–34)

Position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	EcoRV						BanII																PstI
VLκ1	GAT	ATC	CAG	ATG	ACC	CAG	AGC	CCG	TCT	AGC	CTG	AGC	GCG	AGC	GTG	GGT	GAT	CGT	GTG	ACC	ATT	ACC	TGC
VLκ2	GAT	ATC	GTG	ATG	ACC	CAG	AGC	CCA	CTG	AGC	CTG	CCA	GTG	ACT	CCG	GGC	GAG	CCT	GCG	AGC	ATT	AGC	TGC
VLκ3	GAT	ATC	GTG	CTG	ACC	CAG	AGC	CCG	GCG	ACC	CTG	AGC	CTG	TCT	CCG	GGC	GAA	CGT	GCG	ACC	CTG	AGC	TGC
VLκ4	GAT	ATC	GTG	ATG	ACC	CAG	AGC	CCG	GAT	AGC	CTG	GCG	GTG	AGC	CTG	GGC	GAA	CGT	GCG	ACC	ATT	AAC	TGC
VLλ1	GAT	ATC	GTG	CTG	ACC	CAG	CCG	CCT	.	TCA	GTG	AGT	GGC	GCA	CCA	GGT	CAG	CGT	GTG	ACC	ATC	TCG	TGT
VLλ2	GAT	ATC	GCA	CTG	ACC	CAG	CCA	GCT	.	TCA	GTG	AGC	GGC	TCA	CCA	GGT	CAG	AGC	ATT	ACC	ATC	TCG	TGT
VLλ3	GAT	ATC	GAA	CTG	ACC	CAG	CCG	CCT	.	TCA	GTG	AGC	GTT	GCA	CCA	GGT	CAG	ACC	GCG	CGT	ATC	TCG	TGT
	EcoRV														SexAI							BssSI	

Position	24	25	26	27	28	29	30	a	b	c	d	e	f	31	32	33	34	35	36	37	38
																			KpnI		
VLκ1	AGA	GCG	AGC	CAG	GGC	ATT	AGC	AGC	—	—	—	—	—	—	TAT	CTG	GCG	TGG	TAC	CAG	CAG
VLκ2	AGA	AGC	AGC	CAA	AGC	CTG	CTG	CAT	AGC	—	AAC	GGC	TAT	AAC	TAT	CTG	GAT	TGG	TAC	CTT	CAA
VLκ3	AGA	GCG	AGC	CAG	AGC	GTG	AGC	AGC	—	—	—	—	—	AGC	TAT	CTG	GCG	TGG	TAC	CAG	CAG
VLκ4	AGA	AGC	AGC	CAG	AGC	GTG	CTG	TAT	AGC	AGC	AAC	AAC	AAA	AAC	TAT	CTG	GCG	TGG	TAC	CAG	CAG
VLλ1	AGC	GGC	AGC	AGC	AGC	AAC	ATT	GGC	AGC	AAC	—	—	—	—	TAT	GTG	AGC	TGG	TAC	CAG	CAG
VLλ2	ACG	GGT	ACT	AGC	AGC	GAT	GTG	GGC	GGC	TAT	AAC	—	—	—	TAT	GTG	AGC	TGG	TAC	CAG	CAG
VLλ3	AGC	GGC	—	GAT	GCG	—	CTG	GGC	GAT	AAA	—	—	—	—	TAC	GCG	AGC	TGG	TAC	CAG	CAG
																			KpnI		

VH

Framework 1 (positions 1–25) | CDR 1 (positions 26–35) | Frame

Position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
			MfeI																					
VH1A	CAG	GTG	CAA	TTG	GTT	CAG	TCT	GGC	GCG	GAA	GTG	AAA	AAA	CCG	GGC	AGC	AGC	GTG	AAA	GTG	AGC	TGC	AAA	GCC
VH1B	CAG	GTG	CAA	TTG	GTT	CAG	AGC	GGC	GCG	GAA	GTG	AAA	AAA	CCG	GGC	GCG	AGC	GTG	AAA	GTG	AGC	TGC	AAA	GCC
VH2	CAG	GTG	CAA	TTG	AAA	GAA	AGC	GGC	CCG	GCC	CTG	GTG	AAA	CCG	ACC	CAA	ACC	CTG	ACC	CTG	ACC	TGT	ACC	TTT
VH3	CAG	GTG	CAA	TTG	GTG	GAA	AGC	GGC	GGC	GGC	CTG	GTG	CAA	CCG	GGC	GGC	AGC	CTG	CGT	CTG	AGC	TGC	GCG	GCC
VH4	CAG	GTG	CAA	TTG	CAA	GAA	AGT	GGT	CCG	GGC	CTG	GTG	AAA	CCG	AGC	GAA	ACC	CTG	AGC	CTG	ACC	TGC	ACC	GTT
VH5	CAG	GTG	CAA	TTG	GTT	CAG	AGC	GGC	GCG	GAA	GTG	AAA	AAA	CCG	GGC	GAA	AGC	CTG	AAA	ATT	AGC	TGC	AAA	GGT
VH6	CAG	GTG	CAA	TTG	CAA	CAG	TCT	GGT	CCG	GGC	CTG	GTG	AAA	CCG	AGC	CAA	ACC	CTG	AGC	CTG	ACC	TGT	GCG	ATT

Position	25	26	27	28	29	30	31	a	b	32	33	34	35	36	37	38	39	40	41	42
	BspEI																	BstXI		
VH1A	TCC	GGA	GGC	ACT	TTT	AGC	AGC	—	—	TAT	GCG	ATT	AGC	TGG	GTG	CGC	CAA	GCC	CCT	GGG
VH1B	TCC	GGA	TAT	ACC	TTT	ACC	AGC	—	—	TAT	TAT	ATG	CAC	TGG	GTC	CGC	CAA	GCC	CCT	GGG
VH2	TCC	GGA	TTT	AGC	CTG	TCC	ACG	TCT	GGC	GTT	GGC	GTG	GGC	TGG	ATT	CGC	CAG	CCG	CCT	GGG
VH3	TCC	GGA	TTT	ACC	TTT	AGC	AGC	—	—	TAT	GCG	ATG	AGC	TGG	GTG	CGC	CAA	GCC	CCT	GGG
VH4	TCC	GGA	GGC	AGC	ATT	AGC	AGC	—	—	TAT	TAT	TGG	AGC	TGG	ATT	CGC	CAG	CCG	CCT	GGG
VH5	TCC	GGA	TAT	TCC	TTT	ACG	AGC	—	—	TAT	TGG	ATT	GGC	TGG	GTG	CGC	CAG	ATG	CCT	GGG
VH6	TCC	GGA	GAT	AGC	GTG	AGC	AGC	AAC	AGC	GCG	GCG	TGG	AAC	TGG	ATT	CGC	CAG	TCT	CCT	GGG

FIG. 2

Framework 2											CDR 2							Framework 3																											
	4										5										6										7										8				
9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4
	SexAI							AseI											SanDI								BamHI															BbsI			
AAA	CCA	GGT	AAA	GCA	CCG	AAA	CTA	TTA	ATT	TAT	GCA	GCC	AGC	AGC	TTG	CAA	AGC	GGG	GTC	CCG	TCC	CGT	TTT	AGC	GGC	TCT	GGA	TCC	GGC	ACT	GAT	TTT	ACC	CTG	ACC	ATT	AGC	AGC	CTG	CAA	CCT	GAA	GAC	TTT	GCG
AAA	CCA	GGT	CAA	AGC	CCG	CAG	CTA	TTA	ATT	TAT	CTG	GGC	AGC	AAC	CGT	GCC	AGT	GGG	GTC	CCG	GAT	CGT	TTT	AGC	GGC	TCT	GGA	TCC	GGC	ACC	GAT	TTT	ACC	CTG	AAA	ATT	AGC	CGT	GTG	GAA	GCT	GAA	GAC	GTG	GGC
AAA	CCA	GGT	CAA	GCA	CCG	CGT	CTA	TTA	ATT	TAT	GGC	GCG	AGC	AGC	CGT	GCA	ACT	GGG	GTC	CCG	GCG	CGT	TTT	AGC	GGC	TCT	GGA	TCC	GGC	ACG	GAT	TTT	ACC	CTG	ACC	ATT	AGC	AGC	CTG	GAA	CCT	GAA	GAC	TTT	GCG
AAA	CCA	GGT	CAG	CCG	CCG	AAA	CTA	TTA	ATT	TAT	TGG	GCA	TCC	ACC	CGT	GAA	AGC	GGG	GTC	CCG	GAT	CGT	TTT	AGC	GGC	TCT	GGA	TCC	GGC	ACT	GAT	TTT	ACC	CTG	ACC	ATT	TCG	TCC	CTG	CAA	GCT	GAA	GAC	GTG	GCG
TTG	CCC	GGG	ACG	GCG	CCG	AAA	CTG	CTG	ATT	TAT	GAT	AAC	AAC	CAG	CGT	CCC	TCA	GGC	GTG	CCG	GAT	CGT	TTT	AGC	GGA	TCC	AAA	AGC	GGC	ACC	AGC	GCG	AGC	CTT	GCG	ATT	ACG	GGC	CTG	CAA	AGC	GAA	GAC	GAA	GCG
CAT	CCC	GGG	AAG	GCG	CCG	AAA	CTG	ATG	ATT	TAT	GAT	GTG	AGC	AAC	CGT	CCC	TCA	GGC	GTG	AGC	AAC	CGT	TTT	AGC	GGA	TCC	AAA	AGC	GGC	AAC	ACC	GCG	AGC	CTG	ACC	ATT	AGC	GGC	CTG	CAA	GCG	GAA	GAC	GAA	GCG
AAA	CCC	GGG	CAG	GCG	CCA	GTT	CTG	GTG	ATT	TAT	GAT	GAT	TCT	GAC	CGT	CCC	TCA	GGC	ATC	CCG	GAA	CGC	TTT	AGC	GGA	TCC	AAC	AGC	GGC	AAC	ACC	GCG	ACC	CTG	ACC	ATT	AGC	GGC	ACT	CAG	GCG	GAA	GAC	GAA	GCG
	XmaI			BbeI													Bsu36I								BamHI																	BbsI			

work 2							CDR 2																			Framework 3																			
							5													6										7										8					
3	4	5	6	7	8	9	0	1	2	a	b	c	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	a	b	c
		XhoI																									BstEII							NspV											
CAG	GGT	CTC	GAG	TGG	ATG	GGC	GGC	ATT	ATT	CCG			ATT	TTT	GGC	ACG	GCG	AAC	TAC	GCG	CAG	AAG	TTT	CAG	GGC	CGG	GTG	ACC	ATT	ACC	GCG	GAT	GAA	AGC	ACC	AGC	ACC	GCG	TAT	ATG	GAA	CTG	AGC	AGC	CTG
CAG	GGT	CTC	GAG	TGG	ATG	GGC	TGG	ATT	AAC	CCG			AAT	AGC	GGC	GGC	ACG	AAC	TAC	GCG	CAG	AAG	TTT	CAG	GGC	CGG	GTG	ACC	ATG	ACC	CGT	GAT	ACC	AGC	ATT	AGC	ACC	GCG	TAT	ATG	GAA	CTG	AGC	AGC	CTG
AAA	GCC	CTC	GAG	TGG	CTG	GCT	CTG	ATT	GAT				TGG	GAT	GAT	GAT	AAG	TAT	TAT	AGC	ACC	AGC	CTG	AAA	ACG	CGT	CTG	ACC	ATT	AGC	AAA	GAT	ACT	TCG	AAA	AAT	CAG	GTG	GTG	CTG	ACT	ATG	ACC	AAC	ATG
AAG	GGT	CTC	GAG	TGG	GTG	AGC	GCG	ATT	AGC	GGT			AGC	GGC	GGC	AGC	ACC	TAT	TAT	GCG	GAT	AGC	GTG	AAA	GGC	CGT	TTT	ACC	ATT	TCA	CGT	GAT	AAT	TCG	AAA	AAC	ACC	CTG	TAT	CTG	CAA	ATG	AAC	AGC	CTG
AAG	GGT	CTC	GAG	TGG	ATT	GGC	TAT	ATT	TAT				TAT	AGC	GGC	AGC	ACC	AAG	TAT	AAT	CCG	AGC	CTG	AAA	AGC	CGG	GTG	ACC	ATT	AGC	GTT	GAT	ACT	TCG	AAA	AAC	CAG	TTT	AGC	CTG	AAA	CTG	AGC	AGC	GTG
AAG	GGT	CTC	GAG	TGG	ATG	GGC	ATT	ATT	TAT	CCG			GGC	GAT	AGC	GAT	ACC	CGT	TAT	TCT	CCG	AGC	TTT	CAG	GGC	CAG	GTG	ACC	ATT	AGC	GCG	GAT	AAA	AGC	ATT	AGC	ACC	GCG	TAT	CTT	CAA	TGG	AGC	AGC	CTG
CGT	GGC	CTC	GAG	TGG	CTG	GGC	CGT	ACC	TAT	TAT	CGT		AGC	AAA	TGG	TAT	AAC	GAT	TAT	GCG	GTG	AGC	GTG	AAA	AGC	CGG	ATT	ACC	ATC	AAC	CCG	GAT	ACT	TCG	AAA	AAC	CAG	TTT	AGC	GTG	CAA	CTG	AAC	AGC	GTG

FIG. 2, cont.

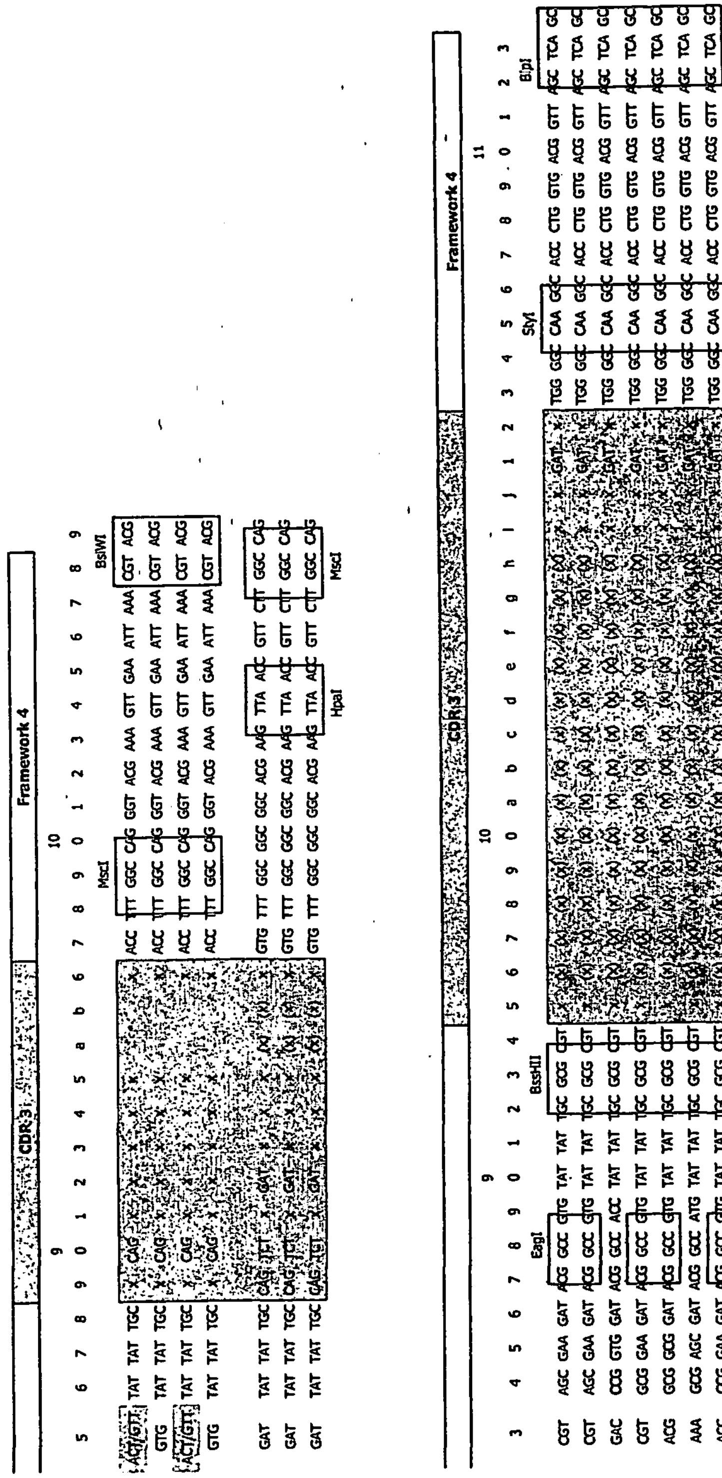

FIG. 2, cont.

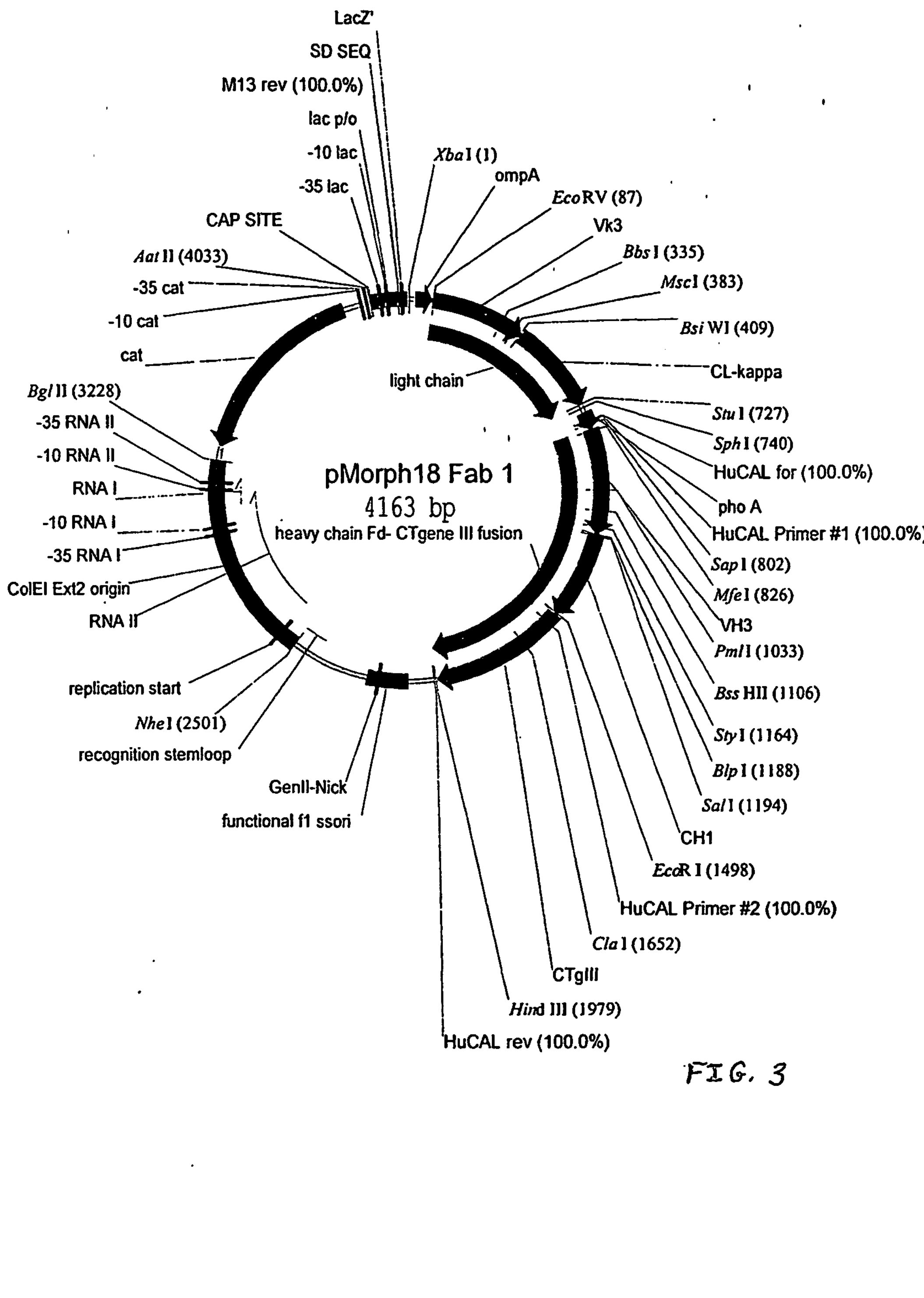
LacZ'
SD SEQ
M13 rev (100.0%)
lac p/o
-10 lac
-35 lac
CAP SITE
AatII (4033)
-35 cat
-10 cat
cat
BglII (3228)
-35 RNA II
-10 RNA II
RNA I
-10 RNA I
-35 RNA I
ColEI Ext2 origin
RNA II
replication start
NheI (2501)
recognition stemloop
GenII-Nick
functional f1 ssori
XbaI (1)
ompA
EcoRV (87)
Vk3
BbsI (335)
MscI (383)
BsiWI (409)
CL-kappa
light chain
StuI (727)
SphI (740)
HuCAL for (100.0%)
pho A
HuCAL Primer #1 (100.0%)
SapI (802)
MfeI (826)
VH3
PmlI (1033)
BssHII (1106)
StyI (1164)
BlpI (1188)
SalI (1194)
CH1
EcoRI (1498)
HuCAL Primer #2 (100.0%)
ClaI (1652)
CTgIII
HindIII (1979)
HuCAL rev (100.0%)
pMorph18 Fab 1
4163 bp
heavy chain Fd- CTgene III fusion

FIG. 3

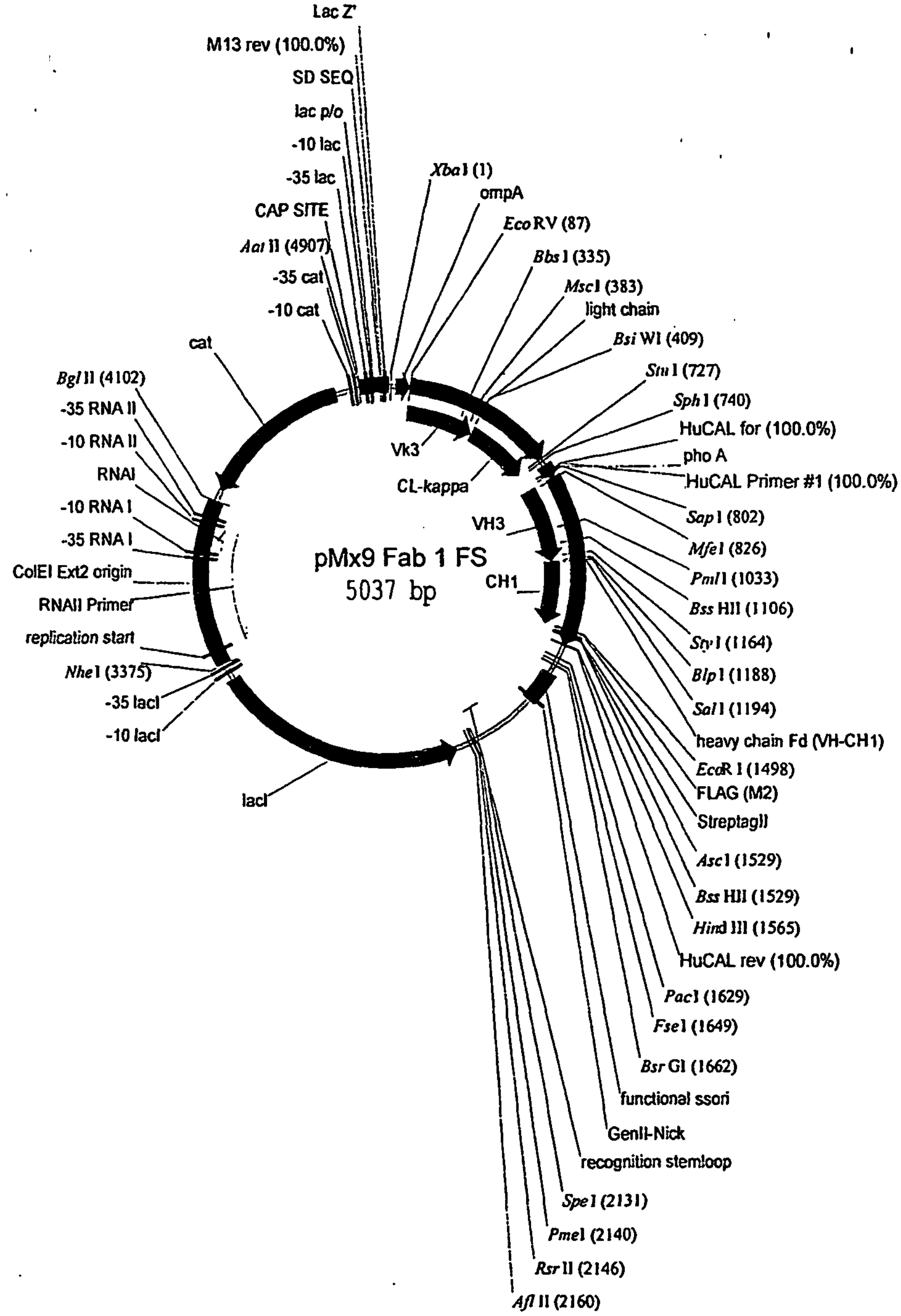
Lac Z'
M13 rev (100.0%)
SD SEQ
lac p/o
-10 lac
-35 lac
CAP SITE
AatII (4907)
-35 cat
-10 cat
cat
BglII (4102)
-35 RNA II
-10 RNA II
RNAI
-10 RNA I
-35 RNA I
ColEI Ext2 origin
RNAII Primer
replication start
NheI (3375)
-35 lacI
-10 lacI
lacI
XbaI (1)
ompA
EcoRV (87)
BbsI (335)
MscI (383)
light chain
BsiWI (409)
StuI (727)
SphI (740)
HuCAL for (100.0%)
pho A
HuCAL Primer #1 (100.0%)
SapI (802)
MfeI (826)
PmlI (1033)
BssHII (1106)
StyI (1164)
BlpI (1188)
SalI (1194)
heavy chain Fd (VH-CH1)
EcoRI (1498)
FLAG (M2)
StreptagII
AscI (1529)
BssHII (1529)
HindIII (1565)
HuCAL rev (100.0%)
PacI (1629)
FseI (1649)
BsrGI (1662)
functional ssori
GenII-Nick
recognition stemloop
SpeI (2131)
PmeI (2140)
RsrII (2146)
AflII (2160)
Vk3
CL-kappa
VH3
CH1
pMx9 Fab 1 FS
5037 bp

FIG. 4

FIG. 5

```
TIMP1_human 135850        1 CTCVPPHPQTAFCNSDLVIRAKFVGTPEVNQTTLYQRYEIKMTKMYKGFQ  50
TIMP1_rat 1174697         1 CSCAPTHPQTAFCNSDLVIRAKFMGSPEIIETTLYQRYEIKMTKMLKGFD  50
                            *.* * *****************.*.**. .************** ***

TIMP1_human 135850       51 ALGDAADIRFVYTPAMESVCGYFHRSHNRSEEFLIAGKLQDGLLHITTCS 100
TIMP1_rat 1174697        51 AVGNATGFRFAYTPAMESLCGYVHKSQNRSEEFLIAGRLRNGNLHITACS 100
                            *.* *.  ** *******.*** *.*.**********.*. * ****.**

TIMP1_human 135850      101 FVAPWNSLSLAQRRGFTKTYTVGCEECTVFPCLSIPCKLQSGTHCLWTDQ 150
TIMP1_rat 1174697       101 FLVPWHNLSPAQQKAFVKTYSAGCGVCTVFPCSAIPCKLESDSHCLWTDQ 150
                            *. **. ** **.. * ***. **  ****** .*****.* .*******

TIMP1_human 135850      151 LLQGSEKGFQSRHLACLPREPGLCTWQSLRSQIA           184
TIMP1_rat 1174697       151 ILMGSEKGYQSDHFACLPRNPDLCTWQYLGVSMTRSLPLAKAEA 194
                            .* *****.** * ***** * ***** *  ..
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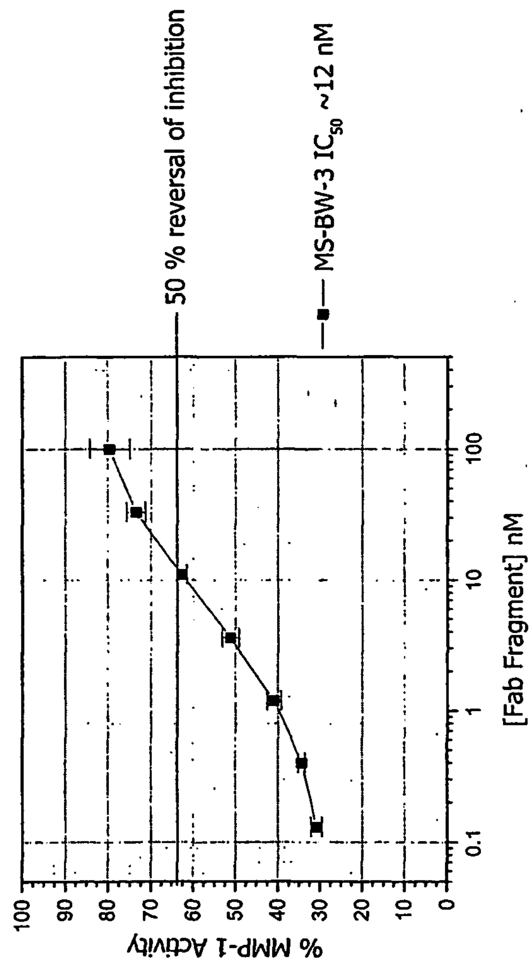

50 % reversal of inhibition
MS-BW-3 IC_{50} ~12 nM
% MMP-1 Activity
[Fab Fragment] nM
0
10
20
30
40
50
60
70
80
90
100
0.1
1
10
100

FIG. 6

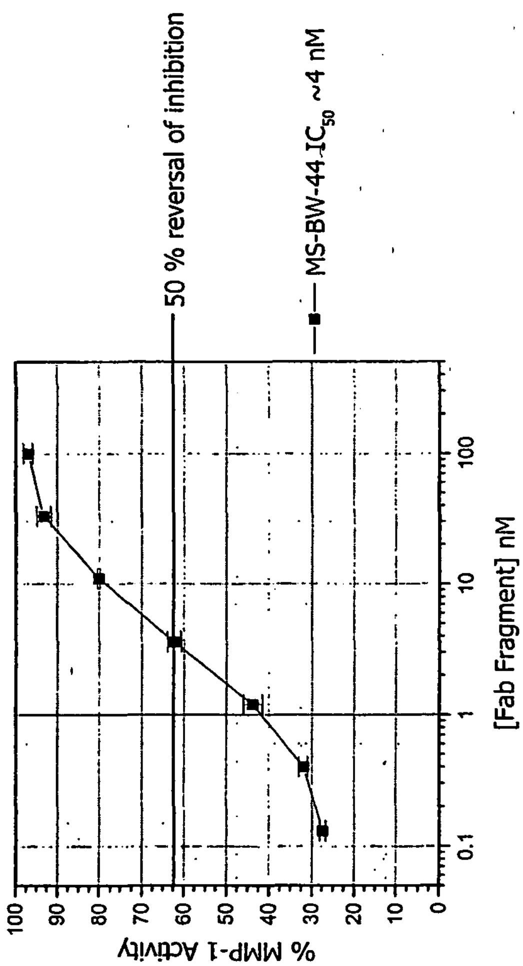

50 % reversal of inhibition
MS-BW-44 IC$_{50}$ ~4 nM
% MMP-1 Activity
100
90
80
70
60
50
40
30
20
10
0
0.1
1
10
100
[Fab Fragment] nM

FIG. 7

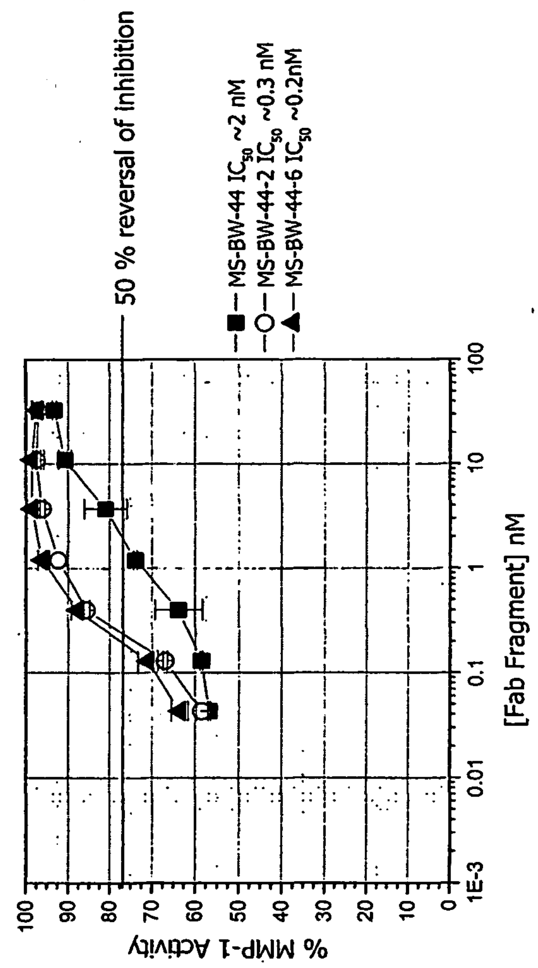

50 % reversal of inhibition
—■— MS-BW-44 IC_{50} ~2 nM
—○— MS-BW-44-2 IC_{50} ~0.3 nM
—▲— MS-BW-44-6 IC_{50} ~0.2nM
% MMP-1 Activity
100
90
80
70
60
50
40
30
20
10
0
1E-3
0.01
0.1
1
10
100
[Fab Fragment] nM

FIG. 8

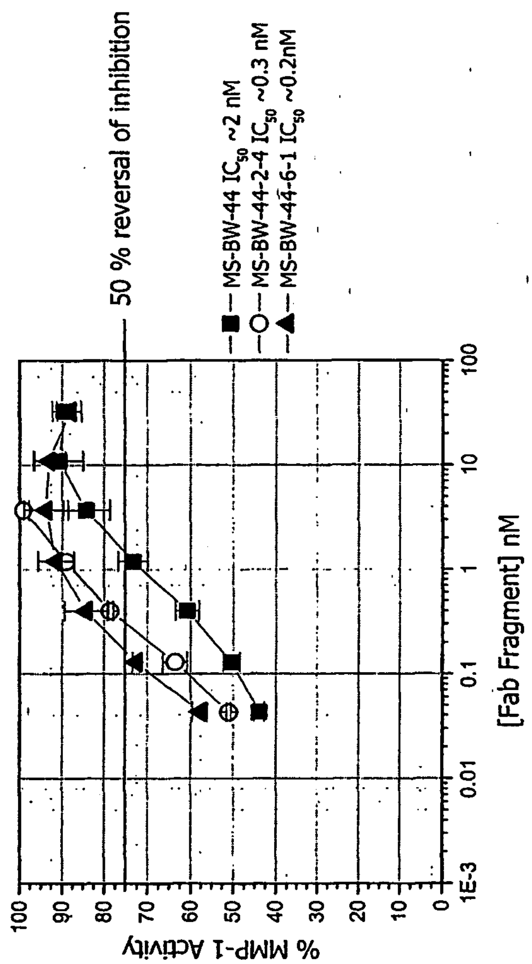

50 % reversal of inhibition
—■— MS-BW-44 IC$_{50}$ ~2 nM
—○— MS-BW-44-2-4 IC$_{50}$ ~0.3 nM
—▲— MS-BW-44-6-1 IC$_{50}$ ~0.2nM
% MMP-1 Activity
[Fab Fragment] nM
0
10
20
30
40
50
60
70
80
90
100
1E-3
0.01
0.1
1
10
100

FIG. 9

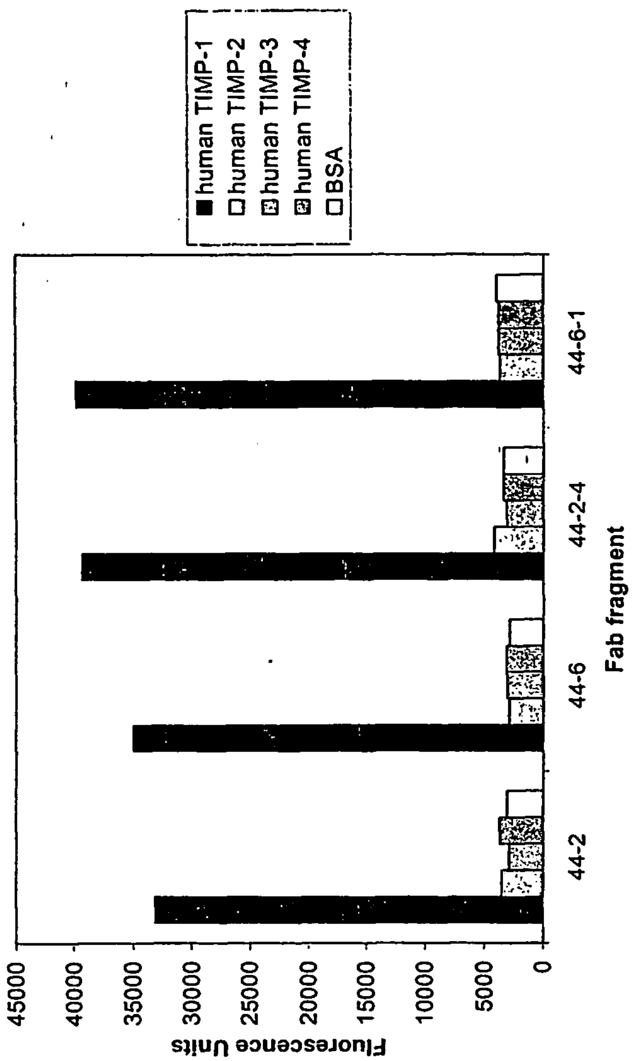

human TIMP-1
human TIMP-2
human TIMP-3
human TIMP-4
BSA
Fluorescence Units
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
44-2
44-6
44-2-4
44-6-1
Fab fragment

FIG. 10

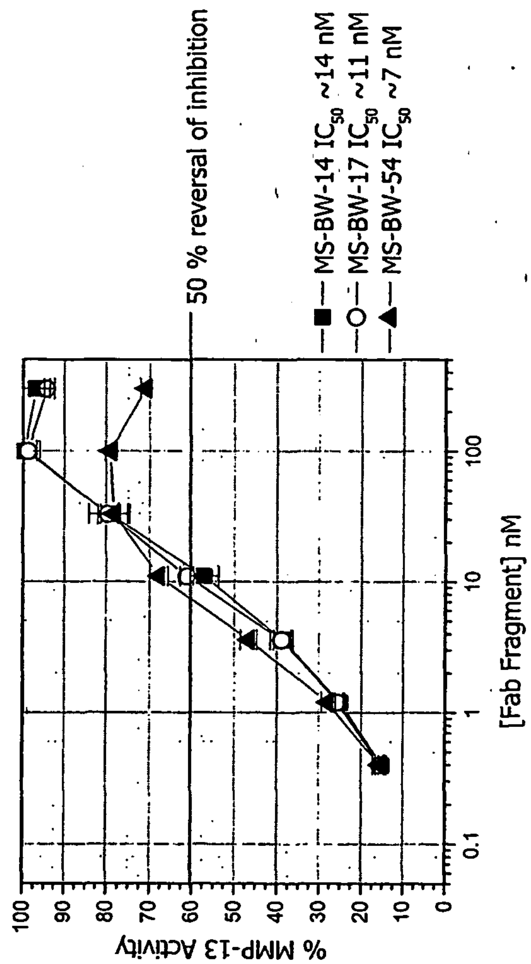

50 % reversal of inhibition
MS-BW-14 IC50 ~14 nM
MS-BW-17 IC50 ~11 nM
MS-BW-54 IC50 ~7 nM
% MMP-13 Activity
100
90
80
70
60
50
40
30
20
10
0
0.1
1
10
100
[Fab Fragment] nM

FIG. 11

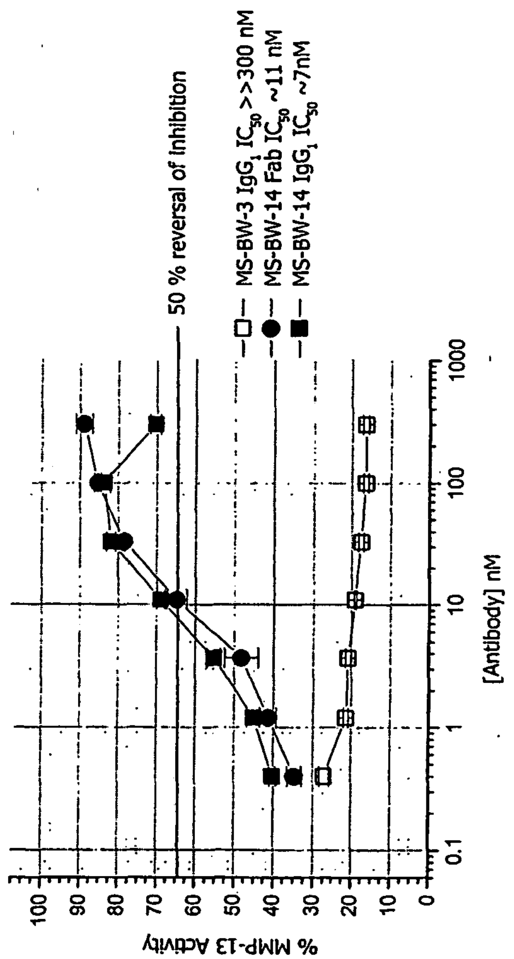

% MMP-13 Activity
[Antibody] nM
50 % reversal of inhibition
MS-BW-3 IgG1 IC50 >>300 nM
MS-BW-14 Fab IC50 ~11 nM
MS-BW-14 IgG1 IC50 ~7nM

FIG. 12

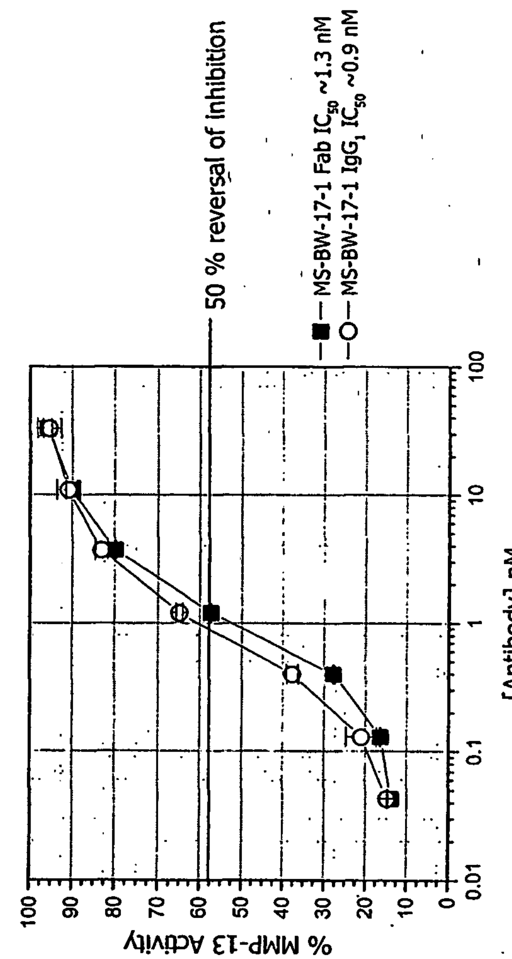

% MMP-13 Activity
100
90
80
70
60
50
40
30
20
10
0
0.01
0.1
1
10
100
[Antibody] nM
50 % reversal of inhibition
MS-BW-17-1 Fab IC_{50} ~1.3 nM
MS-BW-17-1 IgG_1 IC_{50} ~0.9 nM

FIG. 13

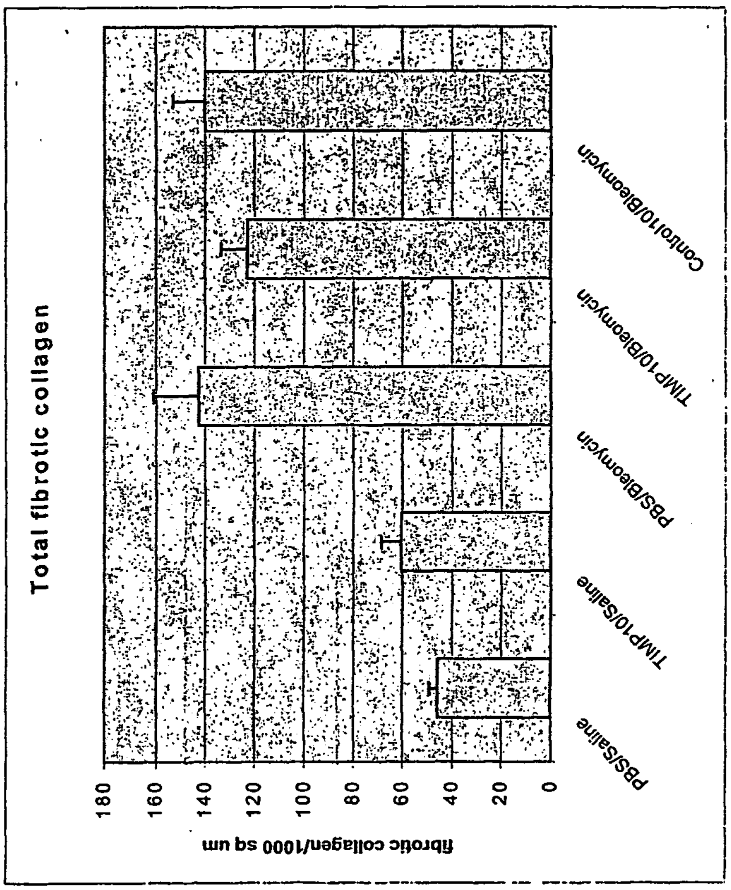
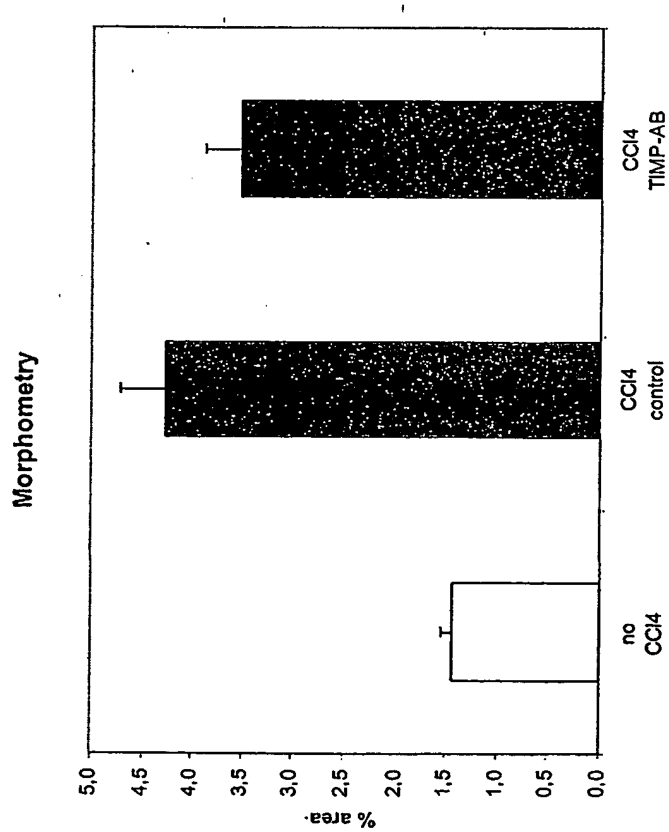

Total fibrotic collagen
fibrotic collagen/1000 sq um
0
20
40
60
80
100
120
140
160
180
PBS/Saline
TIMP10/Saline
PBS/Bleomycin
TIMP10/Bleomycin
Control10/Bleomycin

FIG. 14

FIG. 15


Morphometry
% area
5,0
4,5
4,0
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
no CCl4
CCl4 control
CCl4 TIMP-AB

SEQUENCE LISTING

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MorphoSys AG

<120> Human TIMP-1 Antibodies

<130> 02973.00074

<150> US 60/285,683
<151> 2001-04-24

<160> 381

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Phe Leu Asp Ile
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1 5

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1 5

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Val

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Tyr Gly Ala Tyr Phe Gly Leu Asp Tyr
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1 5 10

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<213> Homo sapiens

<400> 78
Gln Ser Arg Asp Leu Tyr Tyr Val Tyr Tyr
1 5 10

<210> 79
<211> 8
<212> PRT
<213> Homo sapiens

<400> 79
Gln Ser Tyr Asp Arg Ser Met Trp
1 5

<210> 80
<211> 9
<212> PRT
<213> Homo sapiens

<400> 80
Gln Ser Trp Asp Val Gln Thr Asp Lys
1 5

<210> 81
<211> 9
<212> PRT

<213> Homo sapiens

<400> 81
Gln Ser Trp Asp Pro Ser His Tyr Tyr
1 5

<210> 82
<211> 9
<212> PRT
<213> Homo sapiens

<400> 82
Gln Ser Tyr Asp Ile Met Pro Glu Arg
1 5

<210> 83
<211> 9
<212> PRT
<213> Homo sapiens

<400> 83
Gln Ser Met Asp Phe Arg Leu Met His
1 5

<210> 84
<211> 9
<212> PRT
<213> Homo sapiens

<400> 84
Gln Ser Phe Asp Met Ile His Pro Tyr
1 5

<210> 85
<211> 7
<212> PRT
<213> Homo sapiens

<400> 85
Gln Ser Asp Phe Pro Val Met
1 5

<210> 86
<211> 7
<212> PRT
<213> Homo sapiens

<400> 86
Gln Ser Asp Asn Pro Tyr Leu
1 5

<210> 87
<211> 11
<212> PRT
<213> Homo sapiens

<400> 87
Thr Cys Val Pro Pro His Pro Gln Thr Ala Phe
1 5 10

<210> 88
<211> 12
<212> PRT
<213> Homo sapiens

<400> 88
Cys Thr Ser Val Pro Pro His Pro Gln Thr Ala Phe
1 5 10

<210> 89
<211> 12
<212> PRT
<213> Homo sapiens

<400> 89
Ser Thr Cys Val Pro Pro His Pro Gln Thr Ala Phe
1 5 10

<210> 90
<211> 13
<212> PRT
<213> Homo sapiens

<400> 90
Ser Thr Ser Val Pro Pro His Pro Gln Thr Ala Phe Cys
1 5 10

<210> 91
<211> 10
<212> PRT
<213> Homo sapiens

<400> 91
Cys Glu Val Asn Gln Thr Thr Leu Tyr Gln
1 5 10

<210> 92
<211> 12
<212> PRT
<213> Homo sapiens

<400> 92
Pro Ala Met Glu Ser Val Cys Gly Tyr Phe His Arg
 1   5   10

<210> 93
<211> 16
<212> PRT
<213> Homo sapiens

<400> 93
Pro Ala Met Glu Ser Val Cys Gly Tyr Phe His Arg Ser His Asn Arg
 1   5   10   15

<210> 94
<211> 17
<212> PRT
<213> Homo sapiens

<400> 94
Cys Pro Ala Met Glu Ser Val Ser Gly Tyr Phe His Arg Ser His Asn
 1   5   10   15
Arg

<210> 95
<211> 17
<212> PRT
<213> Homo sapiens

<400> 95
Pro Ala Met Glu Ser Val Ser Gly Tyr Phe His Arg Ser His Asn Arg
 1   5   10   15
Cys

<210> 96
<211> 12
<212> PRT
<213> Homo sapiens

<400> 96
Cys Leu Trp Thr Asp Gln Leu Leu Gln Gly Ser Glu
 1   5   10

<210> 97
<211> 215
<212> PRT
<213> Homo sapiens

<400> 97
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Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Gln
                85                  90                  95
Gln Phe Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215
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<210> 98
<211> 215
<212> PRT
<213> Homo sapiens

<400> 98
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Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Lys
                85                  90                  95
Thr Tyr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
```

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115   120   125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130   135   140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145   150   155   160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165   170   175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180   185   190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195   200   205
Thr Val Ala Pro Thr Glu Ala
    210   215

<210> 99
<211> 211
<212> PRT
<213> Homo sapiens

<400> 99
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1   5   10   15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20   25   30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35   40   45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50   55   60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65   70   75   80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Leu
                85   90   95
Arg Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100   105   110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115   120   125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130   135   140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145   150   155   160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165   170   175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180   185   190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195   200   205
Thr Val Ala
    210

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<210> 100
<211> 215
<212> PRT
<213> Homo sapiens

<400> 100
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Ile
                85                  90                  95
Asn Val Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 101
<211> 215
<212> PRT
<213> Homo sapiens

<400> 101
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
```

```
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Val
                85                  90                  95
Arg Phe Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

&lt;210&gt; 102
&lt;211&gt; 215
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 102
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Tyr
                85                  90                  95
Lys Phe Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
```

```
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 103
<211> 215
<212> PRT
<213> Homo sapiens

<400> 103
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Arg
                85                  90                  95
Arg Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 104
<211> 214
<212> PRT
<213> Homo sapiens

<400> 104
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1               5                  10                  15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30
```

```
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Phe Asn Arg
                85                  90                  95
Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145                 150                 155                 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205
Val Ala Pro Thr Glu Ala
    210

<210> 105
<211> 213
<212> PRT
<213> Homo sapiens

<400> 105
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1               5                  10                  15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gln Arg Lys
                85                  90                  95
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
```

```
145                 150                 155                 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205
Ala Pro Thr Glu Ala
    210
```

<210> 106
<211> 215
<212> PRT
<213> Homo sapiens

<400> 106

```
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20                  25                  30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Tyr Gly Thr Ser
                85                  90                  95
Val Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205
Ser Phe Asn Arg Gly Glu Ala
    210                 215
```

<210> 107
<211> 214
<212> PRT
<213> Homo sapiens

<400> 107
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1   5   10   15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20   25   30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35   40   45
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50   55   60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65   70   75   80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gly Phe Lys
                85   90   95
Thr His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100   105   110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115   120   125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130   135   140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145   150   155   160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165   170   175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180   185   190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195   200   205
Val Ala Pro Thr Glu Ala
    210

<210> 108
<211> 211
<212> PRT
<213> Homo sapiens

<400> 108
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1   5   10   15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
            20   25   30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35   40   45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50   55   60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65   70   75   80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Ser Leu Leu Val
                85   90   95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
            100   105   110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Ala
210

<210> 109
<211> 211
<212> PRT
<213> Homo sapiens

<400> 109
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Asn Phe His Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Ala
210

<210> 110
<211> 216
<212> PRT
<213> Homo sapiens

<400> 110
```
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Met Ile
                85                  90                  95
Ala Arg Tyr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205
Lys Thr Val Ala Pro Thr Glu Ala
    210                 215
```

<210> 111
<211> 213
<212> PRT
<213> Homo sapiens

<400> 111
```
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1               5                  10                  15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
```

```
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ile His Pro Phe Asp
                85                  90                  95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205
Ala Pro Thr Glu Ala
    210

<210> 112
<211> 213
<212> PRT
<213> Homo sapiens

<400> 112
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1               5                  10                  15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Leu Glu Pro
                85                  90                  95
Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190
```

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Ala
210

<210> 113
<211> 215
<212> PRT
<213> Homo sapiens

<400> 113
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Leu
85 90 95
Asp Ser Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Ala
210 215

<210> 114
<211> 216
<212> PRT
<213> Homo sapiens

<400> 114
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

```
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Pro Ser
                85                  90                  95
His Pro Ser Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205
Lys Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 115
<211> 214
<212> PRT
<213> Homo sapiens

<400> 115
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asp Met
                85                  90                  95
Gln Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
```

```
145                 150                 155                 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205
Val Ala Pro Thr Glu Ala
    210
```

<210> 116
<211> 215
<212> PRT
<213> Homo sapiens

<400> 116

```
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ile Asn
                85                  90                  95
His Ala Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215
```

<210> 117
<211> 215
<212> PRT
<213> Homo sapiens

<400> 117
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Tyr
85 90 95
Asp Tyr Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Ala
210 215

<210> 118
<211> 215
<212> PRT
<213> Homo sapiens

<400> 118
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ala Asn Asp Phe Pro
85 90 95
Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

```
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205
Ser Phe Asn Arg Gly Glu Ala
    210                 215
```

<210> 119
<211> 216
<212> PRT
<213> Homo sapiens

<400> 119

```
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Asn Leu
                85                  90                  95
Lys Met Pro Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205
Lys Thr Val Ala Pro Thr Glu Ala
    210                 215
```

<210> 120
<211> 216
<212> PRT
<213> Homo sapiens

<400> 120
```
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Phe
                85                  90                  95
Pro Ile Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205
Lys Thr Val Ala Pro Thr Glu Ala
    210                 215
```

<210> 121
<211> 213
<212> PRT
<213> Homo sapiens

<400> 121
```
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
```

```
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Leu Tyr Phe
                85                  90                  95
Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205
Ala Pro Thr Glu Ala
    210

<210> 122
<211> 214
<212> PRT
<213> Homo sapiens

<400> 122
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Thr
                85                  90                  95
Pro Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145                 150                 155                 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190
```

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205
Val Ala Pro Thr Glu Ala
210

<210> 123
<211> 212
<212> PRT
<213> Homo sapiens

<400> 123
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Pro Val Gly Phe Pro
85 90 95
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205
Pro Thr Glu Ala
210

<210> 124
<211> 214
<212> PRT
<213> Homo sapiens

<400> 124
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

```
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Ser
                85                  90                  95
Pro Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145                 150                 155                 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205
Val Ala Pro Thr Glu Ala
    210

<210> 125
<211> 216
<212> PRT
<213> Homo sapiens

<400> 125
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Ser
                85                  90                  95
His Tyr Phe Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
```

```
145                 150                 155                 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205
Lys Thr Val Ala Pro Thr Glu Ala
    210                 215
```

<210> 126
<211> 212
<212> PRT
<213> Homo sapiens

<400> 126

```
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1               5                  10                  15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Arg Tyr Ser His
                85                  90                  95
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
            100                 105                 110
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
        115                 120                 125
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
    130                 135                 140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145                 150                 155                 160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
                165                 170                 175
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
            180                 185                 190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
        195                 200                 205
Pro Thr Glu Ala
    210
```

<210> 127
<211> 214
<212> PRT
<213> Homo sapiens

<400> 127
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Arg
85 90 95
Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205
Val Ala Pro Thr Glu Ala
210

<210> 128
<211> 215
<212> PRT
<213> Homo sapiens

<400> 128
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Thr
85 90 95
Tyr Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

```
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

&lt;210&gt; 129
&lt;211&gt; 215
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 129
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20                  25                  30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe Asn Asp Ser Pro
                85                  90                  95
Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205
Ser Phe Asn Arg Gly Glu Ala
    210                 215
```

<210> 130
<211> 215
<212> PRT
<213> Homo sapiens

<400> 130
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1   5   10   15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20   25   30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35   40   45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50   55   60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65   70   75   80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ile Ser
                85   90   95
Gly Tyr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100   105   110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115   120   125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130   135   140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145   150   155   160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165   170   175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180   185   190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195   200   205
Thr Val Ala Pro Thr Glu Ala
    210   215

<210> 131
<211> 216
<212> PRT
<213> Homo sapiens

<400> 131
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1   5   10   15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20   25   30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35   40   45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50   55   60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Leu Tyr
85 90 95
Tyr Val Tyr Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145 150 155 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205
Lys Thr Val Ala Pro Thr Glu Ala
210 215

<210> 132
<211> 211
<212> PRT
<213> Homo sapiens

<400> 132
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg Ser Met Trp Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190

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Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
        195                 200                 205
Thr Glu Ala
    210

<210> 133
<211> 215
<212> PRT
<213> Homo sapiens

<400> 133
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Val Gln
                85                  90                  95
Thr Asp Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 134
<211> 212
<212> PRT
<213> Homo sapiens

<400> 134
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1               5                  10                  15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
            20                  25                  30
```

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Pro Ser His Tyr Tyr
85 90 95
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205
Pro Thr Glu Ala
210

<210> 135
<211> 215
<212> PRT
<213> Homo sapiens

<400> 135
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ile Met
85 90 95
Pro Glu Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys

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145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 136
<211> 215
<212> PRT
<213> Homo sapiens

<400> 136
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Met Asp Phe Arg
                85                  90                  95
Leu Met His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205
Thr Val Ala Pro Thr Glu Ala
    210                 215

<210> 137
<211> 215
<212> PRT
<213> Homo sapiens
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<400> 137
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Met Ile
85 90 95
His Pro Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Ala
210 215

<210> 138
<211> 213
<212> PRT
<213> Homo sapiens

<400> 138
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Phe Pro Val
85 90 95
Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

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Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205
Ala Pro Thr Glu Ala
    210

<210> 139
<211> 213
<212> PRT
<213> Homo sapiens

<400> 139
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Asn Pro Tyr
                85                  90                  95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205
Ala Pro Thr Glu Ala
    210
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            100                     105                     110
Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
        115                     120                     125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                     135                     140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                     150                     155                     160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                     170                     175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                     185                     190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                     200                     205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                     215                     220
Pro Lys Ser Glu Phe
225

<210> 156
<211> 220
<212> PRT
<213> Homo sapiens

<400> 156
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Ile Gly Tyr Phe Asp Leu Trp Gly Gln Gly Thr Leu Val
            100                 105                 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205
```

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 157
<211> 225
<212> PRT
<213> Homo sapiens

<400> 157
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Leu Thr Asn Tyr Phe Asp Ser Ile Tyr Tyr Asp His Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
210 215 220
Phe
225

<210> 158
<211> 225
<212> PRT
<213> Homo sapiens

<400> 158
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Leu Val Gly Gly Gly Tyr Asp Leu Met Phe Asp Ser Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
210 215 220
Phe
225

<210> 159
<211> 226
<212> PRT
<213> Homo sapiens

<400> 159
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Tyr Val Thr Tyr Gly Tyr Asp Asp Tyr His Phe Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr

    130   135   140
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145   150   155   160
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165   170   175
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180   185   190
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195   200   205
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210   215   220
Glu Phe
225

<210> 160
<211> 219
<212> PRT
<213> Homo sapiens

<400> 160
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20   25   30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50   55   60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Ser Gly Tyr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
        115   120   125
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
    130   135   140
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145   150   155   160
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
                165   170   175
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
            180   185   190
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
        195   200   205
Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210   215

<210> 161

<211> 231
<212> PRT
<213> Homo sapiens

<400> 161
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20   25   30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50   55   60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Tyr Ile Gly Tyr Thr Asn Val Met Asp Ile Arg Pro Gly Phe
            100   105   110
Tyr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
        115   120   125
Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
    130   135   140
Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
145   150   155   160
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
                165   170   175
Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
            180   185   190
Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
        195   200   205
Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
    210   215   220
Val Glu Pro Lys Ser Glu Phe
225   230

<210> 162
<211> 225
<212> PRT
<213> Homo sapiens

<400> 162
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1   5   10   15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20   25   30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35   40   45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50   55   60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Phe Arg Ala Tyr Gly Asp Asp Phe Tyr Phe Asp Val Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
210 215 220
Phe
225

<210> 163
<211> 228
<212> PRT
<213> Homo sapiens

<400> 163
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ile Met Trp Ser Asp Tyr Gly Gln Leu Val Lys Gly Gly Asp
100 105 110
Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125
Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
130 135 140
Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145 150 155 160
Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr

```
                165                 170                 175
Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                 185                 190
Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
        195                 200                 205
Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
    210                 215                 220
Lys Ser Glu Phe
225
```

<210> 164
<211> 224
<212> PRT
<213> Homo sapiens

<400> 164

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Tyr Tyr Val Thr Asp Thr Ala Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220
```

<210> 165
<211> 224
<212> PRT
<213> Homo sapiens

<400> 165
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg His Asp Phe Asp Gly Ser Ile Phe Met Asp Phe Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 166
<211> 225
<212> PRT
<213> Homo sapiens

<400> 166
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Tyr Ala Gly His Gln Tyr Glu Phe Phe Phe Asp Phe Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115   120   125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130   135   140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145   150   155   160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165   170   175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180   185   190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195   200   205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
    210   215   220
Phe
225

<210> 167
<211> 224
<212> PRT
<213> Homo sapiens

<400> 167
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1   5   10   15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20   25   30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35   40   45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50   55   60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65   70   75   80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95
Ala Arg Leu Tyr Ala Asp Ala Asp Ile Tyr Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115   120   125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130   135   140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145   150   155   160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165   170   175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180   185   190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195   200   205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe

210 215 220

<210> 168
<211> 222
<212> PRT
<213> Homo sapiens

<400> 168
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Thr Lys Tyr Val Gly Ser Glu Asp Val Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 169
<211> 222
<212> PRT
<213> Homo sapiens

<400> 169
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Tyr Arg Tyr Pro His Met Phe Asp Phe Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210 215 220

<210> 170
<211> 224
<212> PRT
<213> Homo sapiens

<400> 170
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Leu Phe Ala Gly Leu Glu Leu Tyr Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

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Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 171
<211> 221
<212> PRT
<213> Homo sapiens

<400> 171
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gly Gly Phe Phe Asn Met Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 172
<211> 223
<212> PRT
<213> Homo sapiens

<400> 172
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
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```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gly Tyr Ile Pro Tyr His Leu Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 173
<211> 225
<212> PRT
<213> Homo sapiens

<400> 173
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Tyr Tyr Gly Phe Glu Tyr Asp Leu Leu Phe Asp Asn Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
```

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    130                 135                 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
    210                 215                 220
Phe
225
```

<210> 174
<211> 221
<212> PRT
<213> Homo sapiens

<400> 174

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ile Thr Tyr Ile Gly Tyr Asp Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220
```

<210> 175

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<211> 220
<212> PRT
<213> Homo sapiens

<400> 175
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gln Glu Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 176
<211> 224
<212> PRT
<213> Homo sapiens

<400> 176
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Tyr Pro Glu Asp Leu Ile Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 177
<211> 231
<212> PRT
<213> Homo sapiens

<400> 177
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30
Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50                  55                  60
Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80
Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95
Tyr Tyr Cys Ala Arg Trp Met Thr Pro Pro Gly His Tyr Tyr Gly Tyr
            100                 105                 110
Thr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
        115                 120                 125
Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
    130                 135                 140
Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
145                 150                 155                 160
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
                165                 170                 175
Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
            180                 185                 190
Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
```

```
        195                 200                 205
Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
    210                 215                 220
Val Glu Pro Lys Ser Glu Phe
225                 230

&lt;210&gt; 178
&lt;211&gt; 225
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 178
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Arg Val His Asp Tyr Ala Met Tyr Phe Asp Leu Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
    210                 215                 220
Phe
225

&lt;210&gt; 179
&lt;211&gt; 226
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 179
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
```

```
 1               5                   10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Phe Val Ser Tyr Asn Gly Ser Val Pro Tyr Phe Asp Tyr Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220
Glu Phe
225
```

```
<210> 180
<211> 224
<212> PRT
<213> Homo sapiens

<400> 180
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                   10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Ile Ile Gly Asp Tyr Val Ile Phe Phe Asp Val Trp Gly Gln
            100                 105                 110
```

```
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220

<210> 181
<211> 224
<212> PRT
<213> Homo sapiens

<400> 181
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Leu Phe Thr Tyr Pro Phe Leu Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220
```

<210> 182
<211> 224
<212> PRT
<213> Homo sapiens

<400> 182
```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Ile Leu Thr Gly His Val Leu Leu Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
    210                 215                 220
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<210> 183
<211> 27
<212> DNA
<213> Homo sapiens

<400> 183
cagagctatg actatcagca gtttact 27

<210> 184
<211> 26
<212> DNA
<213> Homo sapiens

<400> 184
cagagctatg actttaagac ttatct 26

<210> 185
<211> 26
<212> DNA
<213> Homo sapiens

<400> 185
cagagctatg actttcttcg tttttc 26

<210> 186
<211> 27
<212> DNA
<213> Homo sapiens

<400> 186
cagagctatg actttattaa tgttatt 27

<210> 187
<211> 27
<212> DNA
<213> Homo sapiens

<400> 187
cagagctatg actttgttcg ttttatg 27

<210> 188
<211> 27
<212> DNA
<213> Homo sapiens

<400> 188
cagagctatg acttttataa gtttaat 27

<210> 189
<211> 27
<212> DNA
<213> Homo sapiens

<400> 189
cagagctatg actttcgtcg tttttct 27

<210> 190
<211> 27
<212> DNA
<213> Homo sapiens

<400> 190
cagagccgtg actttaatcg tggtcct 27

<210> 191

<211> 24
<212> DNA
<213> Homo sapiens

<400> 191
cagagctatg accagcgtaa gtgg 24

<210> 192
<211> 24
<212> DNA
<213> Homo sapiens

<400> 192
cagcagcttt atggtacttc tgtt 24

<210> 193
<211> 27
<212> DNA
<213> Homo sapiens

<400> 193
cagagctatg acggttttaa gactcat 27

<210> 194
<211> 24
<212> DNA
<213> Homo sapiens

<400> 194
cagagctatg actattctct tctt 24

<210> 195
<211> 24
<212> DNA
<213> Homo sapiens

<400> 195
cagagctatg actttaattt tcat 24

<210> 196
<211> 30
<212> DNA
<213> Homo sapiens

<400> 196
cagagctatg acatgattgc tcgttatcct 30

<210> 197
<211> 30
<212> DNA

<213> Homo sapiens

<400> 197
cagagctggg acattcatcc ttttgatgtt 30

<210> 198
<211> 24
<212> DNA
<213> Homo sapiens

<400> 198
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aaaagc 666

<210> 280
<211> 684
<212> DNA
<213> Homo sapiens

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gcggtgctgc aaagcagcgg cctgtatagc ctgagcagcg ttgtgaccgt gccgagcagc 600
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gataaaaaag tggaaccgaa aagc 684

<210> 281
<211> 660
<212> DNA
<213> Homo sapiens

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tgcaacgtga accataaacc gagcaacacc aaagtggata aaaaagtgga accgaaaagc 660

<210> 282
<211> 669
<212> DNA
<213> Homo sapiens

<400> 282
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acctgtgcga tttccggaga tagcgtgagc agcaacagcg cggcgtggaa ctggattcgc 120
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agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag 600
acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 283
<211> 654
<212> DNA
<213> Homo sapiens

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gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
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gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagc 654

<210> 284
<211> 681

<212> DNA
<213> Homo sapiens

<400> 284
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ccagtcaccg tgagctggaa cagcggggcg ctgaccagcg gcgtgcatac ctttccggcg 540
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ttaggcactc agacctatat ttgcaacgtg aaccataaac cgagcaacac caaagtggat 660
aaaaaagtgg aaccgaaaag c 681

<210> 285
<211> 654
<212> DNA
<213> Homo sapiens

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gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
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gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagc 654

<210> 286
<211> 669
<212> DNA
<213> Homo sapiens

<400> 286
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cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat 180
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ccgaaaagc 669

<210> 287
<211> 669
<212> DNA
<213> Homo sapiens

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acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 288
<211> 672
<212> DNA
<213> Homo sapiens

<400> 288
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cagacctata tttgcaacgt gaaccataaa ccgagcaaca ccaaagtgga taaaaaagtg 660
gaaccgaaaa gc 672

<210> 289
<211> 651
<212> DNA
<213> Homo sapiens

<400> 289
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cctgggcagg gtctcgagtg gatgggcggc attattccga tttttggcac ggcgaactac 180
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atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgttctggt 300
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aaccataaac cgagcaacac caaagtggat aaaaaagtgg aaccgaaaag c 651

<210> 290
<211> 687
<212> DNA
<213> Homo sapiens

<400> 290
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ccggcggtgc tgcaaagcag cggcctgtat agcctgagca gcgttgtgac cgtgccgagc 600
agcagcttag gcactcagac ctatatttgc aacgtgaacc ataaaccgag caacaccaaa 660
gtggataaaa aagtggaacc gaaaagc 687

<210> 291
<211> 669
<212> DNA
<213> Homo sapiens

<400> 291
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agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg 120
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acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 292
<211> 678

<212> DNA
<213> Homo sapiens

<400> 292
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<210> 293
<211> 666
<212> DNA
<213> Homo sapiens

<400> 293
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ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc 600
tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaccg 660
aaaagc 666

<210> 294
<211> 666
<212> DNA
<213> Homo sapiens

<400> 294
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aaaagc 666

<210> 295
<211> 669
<212> DNA
<213> Homo sapiens

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acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

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<211> 614
<212> DNA
<213> Homo sapiens

<400> 296
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tggaaccgaa aagc 614

<210> 297
<211> 660
<212> DNA
<213> Homo sapiens

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<210> 298
<211> 660
<212> DNA
<213> Homo sapiens

<400> 298

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<210> 299
<211> 666
<212> DNA
<213> Homo sapiens

<400> 299

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ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc     600
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<210> 300
<211> 657
<212> DNA

<213> Homo sapiens

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ggggcgctga ccagcggcgt gcataccttt ccggcggtgc tgcaaagcag cggcctgtat 540
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<210> 301
<211> 663
<212> DNA
<213> Homo sapiens

<400> 301
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atttgcaacg tgaaccataa accgagcaac accaaagtgg ataaaaaagt ggaaccgaaa 660
agc 663

<210> 302
<211> 669
<212> DNA
<213> Homo sapiens

<400> 302
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acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 303
<211> 657
<212> DNA
<213> Homo sapiens

<400> 303
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<210> 304
<211> 654
<212> DNA
<213> Homo sapiens

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<210> 305
<211> 666
<212> DNA
<213> Homo sapiens

<400> 305
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tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaccg 660
aaaagc 666

<210> 306
<211> 687
<212> DNA
<213> Homo sapiens

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gtggataaaa aagtggaacc gaaaagc 687

<210> 307
<211> 669
<212> DNA
<213> Homo sapiens

<400> 307
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acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 308
<211> 672
<212> DNA
<213> Homo sapiens

<400> 308
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cagacctata tttgcaacgt gaaccataaa ccgagcaaca ccaaagtgga taaaaaagtg 660
gaaccgaaaa gc 672

<210> 309
<211> 666
<212> DNA
<213> Homo sapiens

<400> 309
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aaaagc 666

<210> 310
<211> 609
<212> DNA
<213> Homo sapiens

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<210> 311
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<212> DNA
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aaaagc 666

<210> 312
<211> 645
<212> DNA
<213> Homo sapiens

<400> 312
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<212> DNA
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catgaggggа gcaccgtgga aaaaaccgtt gcgccgactg aggcc 645

<210> 314
<211> 645
<212> DNA
<213> Homo sapiens

<400> 314
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<210> 315
<211> 638
<212> DNA
<213> Homo sapiens

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catgagggga gcaccgtgga aaaaaccgtt gcgccgac 638

<210> 316
<211> 645
<212> DNA
<213> Homo sapiens

<400> 316
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<210> 317
<211> 638
<212> DNA
<213> Homo sapiens

<400> 317

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tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag    120
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg    180
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg    240
caagcggaag acgaagcgga ttattattgc cagagctatg acttttataa gtttaatgtg    300
tttggcggcg gcacgaagtt aaccgttctt ggccagccga aagccgcacc gagtgtgacg    360
ctgtttccgc cgagcagcga agaattgcag gcgaacaaag cgaccctggt gtgcctgatt    420
agcgactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag    480
gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc    540
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg    600
catgagggga gcaccgtgga aaaaaccgtt gcgccgac                            638
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<210> 318
<211> 638
<212> DNA
<213> Homo sapiens

<400> 318

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catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg    180
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg    240
caagcggaag acgaagcgga ttattattgc cagagctatg actttcgtcg tttttctgtg    300
tttggcggcg gcacgaagtt aaccgttctt ggccagccga aagccgcacc gagtgtgacg    360
ctgtttccgc cgagcagcga agaattgcag gcgaacaaag cgaccctggt gtgcctgatt    420
agcgactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag    480
gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc    540
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg    600
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<210> 319
<211> 642
<212> DNA

<213> Homo sapiens

<400> 319
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tcgtgtagcg gcagcagcag caacattggc agcaactatg tgagctggta ccagcagttg 120
cccgggacgg cgccgaaact gctgatttat gataacaacc agcgtccctc aggcgtgccg 180
gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa 240
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tttccgccga gcagcgaaga attgcaggcg aacaaagcga ccctggtgtg cctgattagc 420
gacttttatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480
ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540
ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600
gaggggagca ccgtggaaaa aaccgttgcg ccgactgagg cc 642

<210> 320
<211> 639
<212> DNA
<213> Homo sapiens

<400> 320
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tcgtgtagcg gcagcagcag caacattggc agcaactatg tgagctggta ccagcagttg 120
cccgggacgg cgccgaaact gctgatttat gataacaacc agcgtccctc aggcgtgccg 180
gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa 240
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ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360
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ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480
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agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600
gggagcaccg tggaaaaaac cgttgcgccg actgaggcc 639

<210> 321
<211> 672
<212> DNA
<213> Homo sapiens

<400> 321
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ctgagctgca gagcgagcca gagcgtgagc agcagctatc tggcgtggta ccagcagaaa 120
ccaggtcaag caccgcgtct attaatttat ggcgcgagca gccgtgcaac tggggtcccg 180
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cctgaagact ttgcgactta ttattgccag cagctttatg gtacttctgt tacctttggc 300
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tatccgcgtg aagcgaaagt tcagtggaaa gtagacaacg cgctgcaaag cggcaacagc 480
caggaaagcg tgaccgaaca ggatagcaaa gatagcacct attctctgag cagcaccctg 540
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ggtctgagca gcccggtgac taaatctttt aatcgtggcg aggcctgata agcatgcgta 660

ggagaaaata aa 672

<210> 322
<211> 642
<212> DNA
<213> Homo sapiens

<400> 322
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tcgtgtagcg gcagcagcag caacattggc agcaactatg tgagctggta ccagcagttg 120
cccgggacgg cgccgaaact gctgatttat gataacaacc agcgtccctc aggcgtgccg 180
gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa 240
agcgaagacg aagcggatta ttattgccag agctatgacg gttttaagac tcatgtgttt 300
ggcggcggca cgaagttaac cgttcttggc cagccgaaag ccgcaccgag tgtgacgctg 360
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gacttttatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480
ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540
ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600
gaggggagca ccgtggaaaa aaccgttgcg ccgactgagg cc 642

<210> 323
<211> 633
<212> DNA
<213> Homo sapiens

<400> 323
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tcgtgtagcg gcgatgcgct gggcgataaa tacgcgagct ggtaccagca gaaacccggg 120
caggcgccag ttctggtgat ttatgatgat tctgaccgtc cctcaggcat cccggaacgc 180
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ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag 480
accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg 540
acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaggggagc 600
accgtggaaa aaaccgttgc gccgactgag gcc 633

<210> 324
<211> 633
<212> DNA
<213> Homo sapiens

<400> 324
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60
tcgtgtagcg gcgatgcgct gggcgataaa tacgcgagct ggtaccagca gaaacccggg 120
caggcgccag ttctggtgat ttatgatgat tctgaccgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagagctat gactttaatt ttcatgtgtt tggcggcggc 300
acgaagttaa ccgttcttgg ccagccgaaa gccgcaccga gtgtgacgct gtttccgccg 360

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ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag     480
accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg     540
acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaggggagc     600
accgtggaaa aaaccgttgc gccgactgag gcc                                  633

<210> 325
<211> 648
<212> DNA
<213> Homo sapiens

<400> 325
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tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag     120
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg     180
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg     240
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gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg     360
acgctgtttc cgccgagcag cgaagaattg caggcgaaca aagcgaccct ggtgtgcctg     420
attagcgact tttatccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc     480
aaggcgggag tggagaccac cacaccctcc aaacaaagca acaacaagta cgcggccagc     540
agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc     600
acgcatgagg ggagcaccgt ggaaaaaacc gttgcgccga ctgaggcc                  648

<210> 326
<211> 639
<212> DNA
<213> Homo sapiens

<400> 326
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tcgtgtagcg gcgatgcgct gggcgataaa tacgcgagct ggtaccagca gaaacccggg     120
caggcgccag ttctggtgat ttatgatgat tctgaccgtc cctcaggcat cccggaacgc     180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa     240
gacgaagcgg attattattg ccagagctgg gacattcatc cttttgatgt tgtgtttggc     300
ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt     360
ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac     420
ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga     480
gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg     540
agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag     600
gggagcaccg tggaaaaaac cgttgcgccg actgaggcc                            639

<210> 327
<211> 639
<212> DNA
<213> Homo sapiens

<400> 327
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tcgtgtagcg gcagcagcag caacattggc agcaactatg tgagctggta ccagcagttg     120
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cccgggacgg cgccgaaact gctgatttat gataacaacc agcgtccctc aggcgtgccg 180
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gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540
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gggagcaccg tggaaaaaac cgttgcgccg actgaggcc 639

<210> 328
<211> 645
<212> DNA
<213> Homo sapiens

<400> 328
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tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg 180
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caagcggaag acgaagcgga ttattattgc cagagctatg acgttcttga ttctgaggtg 300
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tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg 600
catgagggga gcaccgtgga aaaaaccgtt gcgccgactg aggcc 645

<210> 329
<211> 648
<212> DNA
<213> Homo sapiens

<400> 329
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aaggcgggag tggagaccac cacaccctcc aaacaaagca acaacaagta cgcggccagc 540
agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc 600
acgcatgagg ggagcaccgt ggaaaaaacc gttgcgccga ctgaggcc 648

<210> 330
<211> 642
<212> DNA
<213> Homo sapiens

<400> 330
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caagcggaag acgaagcgga ttattattgc cagagctatg acgatatgca gtttgtgttt 300
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gaggggagca ccgtggaaaa aaccgttgcg ccgactgagg cc 642

<210> 331
<211> 645
<212> DNA
<213> Homo sapiens

<400> 331
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<210> 332
<211> 645
<212> DNA
<213> Homo sapiens

<400> 332
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<210> 333
<211> 645
<212> DNA
<213> Homo sapiens

<400> 333
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ggtctgagca gcccggtgac taaatctttt aatcgtggcg aggcc 645

<210> 334
<211> 648
<212> DNA
<213> Homo sapiens

<400> 334
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tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
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acgcatgagg ggagcaccgt ggaaaaaacc gttgcgccga ctgaggcc 648

<210> 335
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<212> DNA
<213> Homo sapiens

<400> 335
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<210> 339
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<212> DNA
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<211> 648
<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

<400> 341

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<212> DNA
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<210> 345
<211> 649
<212> DNA
<213> Homo sapiens

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<211> 648
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<211> 633
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<211> 645
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<213> Homo sapiens

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